CLINICAL STUDY PROTOCOL

BAX326 (rFIX)

PHASE 3

BAX326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study

Short Title: BAX326 Continuation

PROTOCOL NUMBER: 251001

EudraCT Nr: 2010-022726-33

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Study Sponsor(s):

Baxalta US Inc.
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Westlake Village, CA 91362

Baxalta Innovations GmbH
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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

Barbara Valenta-Singer, MD
PPD , Clinical Development
Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor´s medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs), as applicable] will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

See SAER form for contact information.

Further details are also available in the study team roster.

For definitions and information on the assessment of these events, refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX326
Name(s) of Active Ingredient(s)	Recombinant Factor IX (FIX)
CLINICAL CONDITION(S)/INDICATION(S)	
Previously treated patients (PTPs) with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B	
PROTOCOL NUMBER	251001
PROTOCOL TITLE	BAX326 (Recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study
Short Title	BAX326 Continuation
STUDY PHASE	Ph 3
PLANNED STUDY PERIOD	
Initiation	April 2011
Completion	Approximately Q4 2016
Duration	The study duration per subject will vary and can be up to a maximum of 68 months, depending on the date of completing BAX326 Pivotal (250901) or BAX326 Pediatric Study (251101) and the date of licensure in the subject's respective country, but will not last beyond December 31, 2016. For newly recruited subjects, the study participation will be up to approximately 100 EDs, or until BAX 326 is licensened in the subject's country, whichever occurs last, but no later than December 31, 2016. However, a limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs.
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• To further evaluate the safety, hemostatic efficacy, and immunogenicity of BAX326, and changes in health-related quality of life (HR QoL) in subjects who completed Pivotal Study 250901 or Pediatric Study 251101 or newly recruited, BAX326 naïve subjects, until BAX326 is licensed in the subject's country or until the accumulation of up to approximately 100 exposure days (EDs) of treatment with BAX326, whichever occurs last	

Objectives	
• To further evaluate safety of BAX 326 in terms of IP-related AEs as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs • To further evaluate the hemostatic efficacy of BAX326 in the prevention and routine prophylaxis of acute bleeding episodes using various prophylactic treatment regimens • To further evaluate the hemostatic efficacy of BAX326 in the management of acute bleeding episodes • To further evaluate immunogenicity for up to approximately 100 EDs to BAX326.[i] To monitor incremental recovery (IR) of BAX326 over time • To evaluate changes in health-related quality of life (HR QoL), Patient Activity Level and health resource use • Exploratory: To correlate pre-infusion thrombin generation assay (TGA) parameters with pre-infusion FIX levels and spontaneous breakthrough bleeds in a subset of subjects receiving twice weekly standard or modified prophylactic treatment, including PK-tailored prophylaxis.	
STUDY DESIGN	
Study Type	Phase 3, open, prospective, uncontrolled, multicenter, multinational
Control Type	Uncontrolled
Study Indication Type	Prevention, Treatment
Blinding Schema	Open label
Study Design	Prospective, open-label, multicenter, uncontrolled, phase 3 study in approximately 100 PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B who have completed Baxter clinical study protocol 250901 (pivotal) or 251101 (pediatric) and approximately 25 BAX326 naïve subjects who are newly recruited.
Planned Duration of Subject Participation	Subjects will participate in this continuation study until BAX326 is licensed in their respective countries, and they have accumulated a total of at least 100 EDs to BAX326, however no later than December 31, 2016. For newly recruited subjects, the study participation will be up to approximately 100 EDs.The total period of study participation per study subject will vary and can be up to a maximum of 68 months, depending on the date of subject enrollment and the product licensure in the countryof the participating subject, but will not last beyond December 31, 2016. However, a limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs.

[i] Subjects who have participated in BAX326 Pivotal Study 250901 or Pediatric Study 251101, and in BAX326 Continuation Study 251001will have accumulated a total of up to approximately 100 EDs in both studies.

Outcome Measures

Primary Outcome Measure

- Adverse events possibly or probably related to IP

Secondary Outcome Measures

- **Hemostatic efficacy**
  - Treatment of bleeding episodes: number of infusions per bleeding episode, overall hemostatic efficacy rating at resolution of bleed
  - Prophylaxis: annualized bleeding rate (ABR)
  - Consumption of BAX326:
    a. Number of infusions and weight-adjusted consumption per month and per year
    b. Weight-adjusted consumption per event (prophylaxis and on-demand)
- **Safety and Immunogenicity**
  - Development of inhibitory and total binding antibodies to FIX
  - Development of antibodies to CHO proteins and rFurin
  - Occurrence of severe allergic reactions, e.g. anaphylaxis
  - Occurrence of thrombotic events
  - Clinically significant changes in routine laboratory parameters (hematology and clinical chemistry) and vital signs
- **PK**
  - Incremental recovery (IR) over time
  - $AUC_{0-\infty}$ (Area under the plasma concentration versus time curve from time 0 to infinity), IR (incremental recovery, T1/2 (elimination phase half-life), MRT (mean residence time), CL (clearance), V_{ss} (Volume of distribution at steady state)[ii]
- **Health Related Quality of Life, Patient Activity Level and Pharmacoeconomic Parameters**

  Changes in the following HR QoL parameters and health resource use:
  - For subjects who are between 2 to 7 years of age (at the time of screening for Study 251101 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects)[iii]:
    a. Generic: PedsQL™ (Parent-proxy versions: age group 2-4 years and age group 5-7 years)
    b. Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)
    c. Patient Activity Level

[ii] If subject receives a PK-tailored dose regimen and did not participate in the PK portion of the BAX326 pivotal or BAX326 surgery study.

[iii] Due to the unavailability of linguistically validated translations of certain HRQoL measures in certain countries, some of these questionnaires may not be administered in all countries participating in this study.

- For subjects who are between 8 to 11 years of age (at the time of screening for Study 251101 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects):
  a. Disease-specific: Haemo-QoL, short version
  b. Generic: PedsQL™ Child version
  c. Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)
  d. Patient Activity Level
- For subjects who are between 12 and 16 years of age (at the time of screening for Study 250901 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects) the following questionnaires will be used:
  a. Disease-specific: Haemo-QoL short version
  b. Generic: PedsQL™
  c. Health utility: EQ-5D
  d. General pain assessment through a visual analog scale (VAS)
  e. Health resource use
  f. Patient Activity Level
- For subjects aged 17 years and older (at the time of screening for Study 250901 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects) the following questionnaires will be used:
  a. Disease-specific: Haem-A-QoL
  b. Generic: SF-36
  c. Health Utility: EQ-5D
  d. General pain assessment through a visual analog scale (VAS)
  e. Health resource use
  f. Patient Activity Level

- **Exploratory Outcome Measures**
  - If applicable, TGA parameters over 72 hours during PK (lag time, time to peak thrombin generation, peak thrombin generation, endogenous thrombin potential [ETP])
  - TGA parameters pre- and post-infusion concurrent with IR determination for FIX and at some selected timepoints during prophylactic treatment

Investigational Product	BAX326, rFIX: o Standard prophylactic regimen at a dose of 50 IU/kg, ranging from 40-60 IU/kg, which may be increased up to 75 IU/kg, if applicable, for subjects ≥ 12 years. The dose range for pediatric PTPs < 12 years will be 40-80 IU/kg; *OR* o Modified prophylaxis as determined by the investigator. The dose can be increased up to 100 IU/kg, if applicable; *OR* o PK-tailored prophylactic administration of BAX326 based on subject's individual PK. The maximum dose is 120 IU/kg; *OR* o On-demand treatment only. The dose to be used for on-demand treatment depends on the severity of the bleed. This treatment option is not applicable for newly recruited subjects. o 75 ± 5 IU/kg at each regular visit to assess IR. o Individual subject treatment and dosing for IR during the optional additional visits for subjects under standard or modified prophylaxis. **Dosage form**: Lyophilized powder and solvent for solution for injection **Dosage frequency**: Twice weekly, or tailored to the individual needs of subjects as determined by the investigator (modified prophylaxis), or PK-tailored, or on-demand. One dose will be given at each of the study visits to assess IR.
Mode of Administration	Intravenous
SUBJECT SELECTION	
Planned Number of Subjects	Approximately 100 adult and pediatric subjects who participated in BAX326 Pivotal Study 250901 or BAX326 Pediatric Study 251101. In addition, at least 25 BAX326 naïve subjects with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B will be newly enrolled.
Inclusion Criteria	
Inclusion Criteria for Subjects Transitioning from Baxter Pivotal Study 250901 or Pediatric Study 251101: • Subject and/or legal representative has/have voluntarily provided signed informed consent. • Subject has completed Baxter Pivotal Study 250901 or Pediatric Study 251101. Subject was 12 to 65 years old at the time of screening for Study 250901 or < 12 years old at the time of screening for Pediatric Study 251101. • Subject has not developed an inhibitory FIX antibody during Baxter Pivotal Study 250901 or Pediatric Study 251101. • Subject is human immunodeficiency (HIV) negative or is HIV+ with a viral load < 200 particles/µL ~ < 400,000 copies/mL. • Subject is immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm^3. • If female of childbearing potential, subject presents with a negative pregnancy test and agrees to continue employing adequate birth control measures for the duration of the study. • Subject is willing and able to comply with the requirements of the protocol.	

Inclusion criteria for Newly Recruited Subjects:

- Subject and/or legal representative has/have provided signed informed consent.
- Subject is 2 to 70 years old at the time of screening.
- Subject is naïve to BAX326
- Subject has severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B (based on the one stage activated partial thromboplastin time [aPTT] assay), as tested at screening at the central laboratory.
- Subject aged ≥ 6 years is previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 EDs.
- Subject aged < 6 years year is previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.
- Subject has no evidence of a history of FIX inhibitors.
- Subject is immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm3 at screening.
- Subject is human immunodeficiency (HIV) negative or is HIV+ with a viral load < 200 particles/µL ~ < 400,000 copies/mL
- If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
- Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Exclusion Criteria for Subjects Transitioning from Baxter Pivotal Study 250901 or Pediatric Study 251101:

- Subject received FIX product(s) other than BAX326 upon completion of Baxter Pivotal Study 250901 or Pediatric Study 251101.
- Subject has been diagnosed with an acquired hemostatic defect other than hemophilia B.
- For subjects transferring from Pivotal Study 250901: The subject's weight is < 35 kg or > 120 kg.
- Subject's platelet count is < 100,000/mL.
- Subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).
- Subject has active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 5 times the upper limit of normal.
- Subject is scheduled to receive during the course of the study, an immunomodulating drug (e.g. corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
- Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
- Subject is planned to take part in any other clinical study during the course of the Continuation Study, with the exception of BAX326 Surgery Study[iv] as described in this protocol.

[iv] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

- Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

Exclusion Criteria for Newly Recruited Subjects:

- Subject has a history of FIX inhibitors with a titer ≥ 0.6 Bethesda Units (BU) (as determined by the Nijmegen modification of the Bethesda assay or the assay employed in the respective local laboratory) at any time prior to screening.
- Subject has a detectable FIX inhibitor at screening, with a titer ≥ 0.6 BU as determined by the Nijmegen modification of the Bethesda assay in the central laboratory.
- Subjects ≥ 12 years of age: Subject's weight is < 35 kg or > 120 kg
- Subject has a history of allergic reaction, eg, anaphylaxis, following exposure to FIX concentrate(s).
- Subject has a known hypersensitivity to hamster proteins or rFurin.
- Subject has evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
- Subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).
- Subject has severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4 hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.
- Subject has active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 5 times the upper limit of normal.
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.
- Subject's platelet count is < 100,000/mL.
- Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
- Subject is currently receiving, or is scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
- Subject has participated in another investigational study within 30 days of enrollment.
- Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size is not based on statistical consideration and is determined by the number of subjects in Studies 250901 and 251101 who are willing to participate in this Continuation Study 251001 and meet the eligibility criteria as well as regulatory requirements.

Planned Statistical Analysis

The Full Analysis Set (FAS) will be comprised of all subjects who are exposed to any amount of IP. For subjects who discontinue before reaching 100 EDs, data will be included up through the day of discontinuation. The FAS will be used for all analyses.

The pediatric (< 12 years) and the adolescent/adult (≥ 12 years) data will be summarized separately, if appropriate. Further analyses will occur between the age cohorts < 6 years and 6 to < 12 years, if applicable.

Safety and efficacy data from the additional BAX326 naïve subjects (Cohort 2) will be analyzed together with the data from the previously treated subjects (Cohort 1).

The occurrence of IP-related AEs will be evaluated descriptively.

Frequency counts and percentages will be calculated for the following variables: occurrence of inhibitory and total binding antibodies to FIX, occurrence of antibodies to CHO proteins and rFurin, occurrence of severe allergic reactions (e.g., anaphylaxis), and occurrence of thrombotic events.

The following PK parameters for FIX will be reported using descriptive statistics: $AUC_{0-\infty}$, T1/2, MRT, CL, IR, and V_{ss}.

Incremental recovery (IR) will be summarized by visit and displayed graphically over time for each subject. Also the change from the baseline at screening visit will be described using summary statistics.

TGA parameters (lag time, time to peak thrombin generation, peak thrombin generation, and ETP) will be presented descriptively and displayed graphically.The efficacy of BAX326 in the treatment of bleeding episodes will be summarized. It includes the overall hemostatic efficacy rating at resolution of bleed, the number of infusions and the total weight-adjusted dose per bleeding episode.

The annualized rate of bleeding episodes (ABR) will be calculated by treatment regimen, only for subjects who have adequate treatment time for bleeding rate assessment.

Product consumption of BAX326 will be summarized, including the average number of infusions, the average weight-adjusted consumption per months and per year, as well as the average weight-adjusted consumption per event (prophylactic infusion and bleeding treatment).

HR QoL assessment and the change from the baseline will be summarized by visit. Analysis of patient activity level and pharmacoeconomic parameters will be descriptive in nature.

An interim safety review may be performed after a minimum of 50 subjects have accumulated a total of at least 100 EDs to BAX326 for evaluation of long-term hemostatic efficacy, safety, immunogenicity and HrQoL.

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Tables

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time 0 to infinity
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration versus time curve
BDS	Bulk Drug Substance
BU	Bethesda Unit
CHO	Chinese hamster ovary
CIC	Circulating immune complexes
CRM	Cross-reacting material
CSR	Clinical study report
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EC	Ethics committee
ED	Exposure day
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency (previously: EMEA)
EMEA	European Medicines Agency (now: EMA)
ETP	Endogenous thrombin potential
FAS	Full analysis set
FDP	Finished Drug Product
FIX	Factor IX
GCP	Good clinical practice
HAV	Hepatitis A virus
anti-HBs	Antibody to hepatitis B surface antigen
anti-HBc	Antibody to hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

Abbreviation	Definition
HR QoL	Health-related quality of life
hs-CRP	High-sensitive C-reactive protein
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IP	Investigational product
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International units
MRT	Mean residence time
NMC	Non-medical complaint
NOAEL	No observable adverse event level
PK	Pharmacokinetic
PTP	Previously treated patients
SAE	Serious adverse event
SAER	Serious adverse event report
SD	Standard deviation
S/D	Solvent-detergent (virus clearance process)
SIC	Subject identification code
SPC	Summary of product characteristics
SWFI	Sterile water for injection
T1/2	Elimination phase half-life
TGA	Thrombin generation assay
VAS	Visual analog scale
V_{ss}	Volume of distribution at steady state

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta) has developed a recombinant human factor IX (rFIX) product named BAX326 intended for use as both on demand and prophylactic treatment of hemophilia B patients as well as for surgical prophylaxis. BAX326 is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. No materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product, thus reducing the risk of transmission of adventitious agents. The growth medium is a chemically defined medium developed by Baxalta, and the downstream process does not use monoclonal antibodies for the purification of BAX326.

Currently there is only one recombinant FIX product on the market for the treatment of patients with hemophilia B BeneFIX, manufactured by Wyeth (recently acquired by Pfizer).

Physiochemical characterization studies demonstrate that the structure, identity, purity, potency, and functional integrity of BAX326 are comparable to those of BeneFIX. The polypeptide sequence of BAX326 is identical to that of BeneFIX and the post–translational modifications are comparable. The purity and specific activity (in units of clotting activity per mg of total protein) of BAX326 are within the same range as that found for BeneFIX. Preclinical in vivo studies demonstrate that BAX326 and BeneFIX have comparable safety and efficacy profiles. Efficacy was comparable between BAX326 and BeneFIX in primary pharmacodynamic studies in murine models of hemostasis. General safety pharmacology evaluations did not find negative effects of BAX326 on respiratory and cardiovascular parameters. Rabbits treated with BAX326 and BeneFIX showed comparable scores in a study of thrombogenic potential. Pharmacokinetic (PK) evaluations demonstrated similar PK profiles of BAX326 and BeneFIX in mice, rats and monkeys. Taken together, these results demonstrate that the pharmacologic behavior of BAX326 in humans can be expected to be comparable to that of BeneFIX. Also, in all single dose and repeat dose toxicity studies where BAX326 was compared to BeneFIX, Baxalta's recombinant FIX was as well tolerated as the licensed product.

The manufacturing process of BAX326 is comparable to that of BeneFIX but differentiated by the inclusion of two independent viral inactivation/reduction steps, ie, (nanofiltration and solvent/detergent treatment).

Clinical data with BAX326 have been generated in the completed Phase 1/3 pivotal study (Study 250901), the completed Phase 2/3 study 251101 in pediatric PTPs < 12 years of age and the completed Phase 3 surgery study 251002 (see Section 6.4.2).

This open-label study will further evaluate the safety, immunogenicity, and hemostatic efficacy of BAX326 in those subjects who have completed Baxter Protocol 250901 (BAX326 Pivotal) or Baxter Protocol 251101 (BAX326 Pediatric) and who continue meeting the eligibility criteria and in at least 25 newly enrolled, BAX 326 naïve subjects.

The dose of 75 ± 5 IU FIX/kg for the recovery studies is based on the recommendation of the current and newly adapted European Medicines Agency (EMA) guidelines which suggest 50-75 IU/kg.[1;2] The suggested dose regimen for prevention and treatment of bleeding episodes in this study are supported by clinical data of BeneFIX reported for adult and pediatric subjects, including the BeneFIX Summary of Product Characteristics (SPC) [3] and published literature of BeneFIX.[4;5;6]

The recommended IR to be used for calculating the dose for the treatment of bleeding episodes is 0.9 [IU/dL]/[IU/kg] for subjects ≥ 12 years based on the following results from the BAX326 pivotal study: the initial mean IR at C_{max} was 0.87±0.22, the median 0.88 (range of 0.53 to 1.35). The mean IR at the repeat PK was consistent with 0.95±0.25 and a median of 0.93 ranging from 0.52 to 1.38.

The anticipated IR for subjects < 12 years of age is 0.7 [IU/dL]/[IU/kg] , which is based on published literature of BeneFIX and the BeneFIX prescribing information.

Please note: Individualization of the dose is necessary due to the large inter-individual differences in IR for BAX326 and BeneFIX.

The age-related differences in IR should also be considered when calculating the dose for the treatment of bleeding episodes as shown in the following studies reported in the literature:

In a study by Roth et al. with 7362 infusions of BeneFIX in 56 subjects (aged 4-56 years) with severe or moderate hemophilia B [4], IR was 0.75 [IU/dL]/[IU/kg], which was 30% lower than that of plasma-derived FIX concentrates. IR has been found to increase with age, but there was considerable inter-individual variation, indicating that individual dose titration is important.[7] The mean IR for subjects < 15 years was 0.66 ± 0.22 (range 0.34 to 1.12), for subjects aged 15-40 years 0.77 ± 0.20 (range 0.4 to 1.28), and for subjects > 40 years old the mean IR was 0.84 ± 0.27 (range 0.52 to 1.38).

Mean elimination half-life was 19.3 hours (range 11.1 to 36.4). During the course of the study, the dose was increased in 31 PTPs because of low recovery observed at baseline, suboptimal clinical response or breakthrough bleeds during prophylaxis. Sixteen subjects were < 15 years old, which was the cohort with a lower recovery. The mean half-life was similar to that reported for plasma-derived FIX. PK parameters were stable over time. All 1796 hemorrhages were successfully controlled; 81% only required one infusion. One subject developed a low titer inhibitor (1.2 BU) that spontaneously resolved. Similar results were reported by White et al [8]; 80% of the 1070 hemorrhages in 56 patients resolved after one infusion and recovery was 0.8%.

Bjorkman et al. investigated the age-related changes on the PK parameters after administration of rFIX at a dose of 50 IU/kg and the potential impact on dosing for prophylactic treatment based on single-dose curves using computer simulation to predict peak and trough levels of FIX.[7] The single-dose curves were generated in a total of 56 patients.[8] These patients were 4-56 years old, and 46 had severe and 10 had moderate haemophilia B. The analysis showed that age-related changes in Vss and CL of FIX depend mainly on the body weight of the patient and that the $T_{1/2}$ of FIX does not change with age, while IR tends to increase. IR varied from

- 0.61 ± 0.21 in subjects aged 4-9 years (n = 11),
- 0.79 ± 0.27 in subjects aged 10-19 years (n = 10)
- 0.67 ± 0.19 in subjects aged 20-29 years (n = 12)
- 0.84 ± 0.15 in subjects aged 30-39 years (n = 12)
- 0.80 ± 0.29 in subjects aged 40-49 years (n = 7), and
- 0.88 ± 0.23 in subjects aged 50-56 (n = 3).

The mean values for half-life in the age group from 4-9 years and 10-19 years were 20 ± 42 and 20 ± 41 hours, respectively, and comparable to subjects > 19 years. Large inter-individual variability in the disposition of FIX emphasizes the need for individual dose titration. The authors concluded that trough levels of 1% could normally be maintained by dosing every 2-3 days.

In a study performed by Lambert et al. of reformulated BeneFIX (a more concentrated formulation), the bioequivalence of the original and reformulated BeneFIX products was evaluated in PTPs with moderately severe to severe hemophilia B using a double-blind, randomized, crossover study design.[5] The age range was 12-61 years. The reformulated product was bioequivalent to the original product (the mean area under the FIX activity-time curve from time zero to the last measurable activity was 792 h*IU/dL with the original formulation and 851 h*IU/dL for the reformulated BeneFIX).

The efficacy and safety profile remained favorable, with 81% of hemorrhages resolving after a single infusion and an overall spontaneous bleeding rate of 0.72/year. No inhibitor development or allergic reactions occurred. PK of reformulated BeneFIX was analyzed by age. On average, a lower mean IR was found for younger subjects, ie, ≤ 15 years of age (n = 7 subjects; IR = 0.66 ± 0.16, range 0.44 to 0.92) compared with older subjects, ie, > 15 years of age (n = 15 subjects; IR = 0.78 ± 0.19, range 0.39 to 1.2).

The IR of FIX was also studied in a Canadian post-licensure surveillance on the safety of BeneFIX.[9] The mean IR for rFIX for patients aged ≤ 15 years (n = 41) was 0.64 ± 0.11 as compared to patients > 15 years (n = 85) who had a mean IR of 0.84 ± 0.21. Two of 244 subjects treated for up to 5 years with BeneFIX developed inhibitors and anaphylaxis. Both subjects had gene deletions. No thrombotic events were reported.

An international, multicentre, open-label safety and efficacy study of BeneFIX was carried out in 25 patients, regardless of previous treatment, aged < 6 years with severe (FIX:C < 1 IU/dL) hemophilia B.[10] Seven subjects were < 2 years, 18 were between 2-6 years of age. The mean IR, measured at baseline and at the end of treatment (6-12 months after baseline), was 0.58 ± 0.09 and 0.61 ± 0.10, respectively. In a study performed in 63 PUPs with severe or moderately severe hemophilia B, aged < 1 month up to 14 years of age, the mean FIX recovery was 0.68 ± 27 and remained constant over 5 years.[11] It was similar in infants (1 month to < 2 years of age) and children (2 to < 12 years of age): 0.66 ± 0.36 and 0.68 ± 0.21, respectively.

Prophylactic treatment

The suggested dose for prophylactic treatment in patients ≥ 12 years of age is 50 IU/kg twice weekly, ranging from 40-60 IU/kg, which may be increased to 75 IU/kg, if applicable. In the BAX326 pivotal study, the suggested standard prophylactic dose regimen for subjects ≥ 12 years of age was confirmed, as the median dose was 50.5 IU/kg ranging from 40 to 63 IU/kg (mean 49.5±4.8 IU/kg).

For pediatric patients the suggested dose is 50 IU/kg twice weekly, ranging from 40-80 IU/kg, with dose and dosing frequency adjustments depending on the individual recovery and clinical response. The suggested dose is based on studies performed with BeneFIX in pediatric PTPs as well as in PUPs.[10;11]

In a multicenter study performed by Monahan et al., 25 patients, aged < 6 years with severe hemophilia B, regardless of previous treatment, received BeneFIX for the treatment of bleeding episodes and/or prophylaxis (intermittent, routine, and/or surgery related) over 6 to 12 months.[10] Of the 25 subjects, 22 received routine prophylaxis once (n = 9) or twice (n = 12) weekly. One subject received 1-2 infusions per week. The median dose for routine prophylaxis and intermittent infusions was 57.6 IU/kg rFIX, ranging from 27.9 to 187.2 IU/kg. The mean dose was 64.6 ± 22.3 IU/kg. Investigator-prescribed routine prophylaxis included once weekly infusions with doses ranging from 42 to 105 IU/kg (n = 9), 1-2 infusions per week with a dose of 100 IU/kg (n = 1). Most patients (n = 12) had twice weekly infusions with doses ranging from 33 to 87 IU/kg. Near complete prevention of spontaneous breakthrough hemorrhages (< 1 per year) was obtained after routine prophylaxis with 1 or 2 rFIX infusions per week. In a study performed by Shapiro et al. in 63 PUPs with severe or moderately severe hemophilia B < 1 month to 14 years of age, 42 patients received rFIX for routine or intermittent prophylaxis.[11] The median dose was 60.60 IU/kg, ranging from 9.70 to 230.40 IU/kg, and a mean of 71.57 ± 36.89 IU/kg. Of the 32 patients who were on routine prophylaxis, 24 received rFIX ≥ 2 times per week with a mean dose of 72.5 ± 37.1 IU/kg. The remaining 8 patients received rFIX once weekly with a mean dose of 75.9 ± 17.9 IU/kg. The percentage of patients who had early spontaneous breakthrough bleeds was lower in those who received 2 or more infusions per week (3 of 24; 13%) compared with those receiving 1 infusion per week (2 of 8 patients: 25%). In addition, hemostatic efficacy and safety of a PK-tailored treatment regimen, which is based on the subject's individual PK, will be evaluated in this study. The target is to maintain FIX activity levels in plasma of at least 1% above the subject's individual FIX level observed at baseline, ie, at screening of the parent study or, in case of newly recruited subjects, at screening of this study. It is expected that the most commen frequency will be twice weekly. The dose is not to exceed 100 IU/kg.

Patients with moderate hemophilia, ie, FVIII or FIX levels between 1-5%, have fewer hemarthroses, usually trauma-induced, and a decreased likelihood of developing arthropathy than patients with severe hemophilia with FVIII/FIX activity levels < 1%. This observation led to the use of prophylactic infusions to convert a patient from a severe to a moderate bleeding phenotype. Although FVIII or FIX activity levels of 1% are generally considered as protective levels and help identify clear targets, it does not necessarily mean that these levels are the correct baseline level for an individual patient. In a pooled analysis of 143 pediatric and adult patients who had received Advate, a clear correlation between increased total bleeds and hemarthrosis and time spent with a FVIII activity level < 1% could be demonstrated.

Further analyses revealed that half-life and dose frequency had a larger impact on FVIII trough levels and time spent with a FVIII level below 1% per week than incremental recovery or the infused dose/kg.[12;13;14] It is expected that these findings also apply to subjects with severe or moderately severe hemophilia B.

The approach of a PK-tailored prophylactic dosing regimen takes the generally observed marked inter-patient variability of pharmacokinetic parameters into account since dose and frequency will be based on the subject's individual PK. It is expected that by ensuring a FIX level of at least 1% above baseline the frequency of bleeding episodes may be substantially reduced.

6.2 Clinical Condition/Indication

Hemophilia B is an X-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation FIX. Its prevalence is approximately 20% of that of hemophilia A with an incidence of 1 in 30,000 live male births.[15] The severity of both hemophilia A and B is classified according to plasma procoagulant levels, with levels < 1% of normal defined as severe, between 1% and 5% classified as moderate, and > 5% to < 40% defined as mild.[9] Approximately 30 to 45% of persons affected have severe hemophilia B.[16] Plasma-derived and, more recently, recombinant FIX products have been successfully used both prophylactically and to treat bleeding episodes.

There are differences in the severity of the clinical phenotype of patients with hemophilia A and B. The phenotype often does not always reflect the measured procoagulant concentrations in plasma.[17] Hemophilia B patients tend to bleed less, undergo fewer arthroplasties, and require less intense prophylaxis than hemophilia A patients with similar plasma concentrations of the respective factor. Schulman et al devised a Hemophilia Severity Score consisting of annual incidence of joint bleeds, the WFH Orthopedic joint score, and the annual consumption of factor of adult patients with hemophilia A and B at their hospital in Sweden.[18] The median score was higher in patients with severe hemophilia A than severe hemophilia B (median 0.50 versus 0.29), indicating more severe disease in hemophilia A patients. Pai et al investigated the frequency of bleeding and clotting factor use in hemophilia A and B patients: patients with hemophilia B had 35% fewer bleeds than hemophilia A patients, but concentrate use per bleed was similar.[19] In a survey of 2663 hemophilia patients in Canada by Biss et al, 23% of hemophilia A patients and 11% of hemophilia B patients received prophylaxis (ie,, a concentrate infusion at least once a week for ≥ 45 weeks of the year).[6] Tagariello et al. found that patients in Italy with hemophilia A had a 3-fold higher risk of undergoing joint arthroplasty than patients with hemophilia B.[20]

The most serious complication of the disease is the development of inhibitory antibodies that neutralize the coagulatory activity of the infused factor concentrate; this occurs in 1.5 to 3% of patients with hemophilia B.[21;22;23;24;25] Inhibitor development is more common in patients with hemophilia A, with about 30% of patients with severe hemophilia A developing inhibitors. As inhibitor development is relatively rare in hemophilia B there is sparse data on risk factors or the immunological processes involved. An increased incidence of inhibitor development has been seen in patients with certain genetic mutations [26]: those with complete deletions or rearrangements have a higher risk of developing inhibitors than those with nonsense or frame-shift mutations. Furthermore, more patients with hemophilia B than with hemophilia A have been found to be cross-reacting material positive (CRM+) on the basis of detectable FIX antigen.[24] Since fewer CRM+ than CRM- individuals with hemophilia B develop inhibitors, it is further postulated that patients with detectable FIX polypeptide (CRM+) develop tolerance to the 'self' protein that may extend to the exogenous FIX found in replacement therapy.[24;27]

Inhibitors reduce the IR and half-life of FIX, resulting in relative or complete refractoriness to replacement therapy. Although inhibitory alloantibodies to FIX are far less frequently encountered in patients with hemophilia B than those to FVIII in hemophilia A, their onset may be complicated by anaphylaxis if hemophilia B patients are re-exposed to FIX.[28;29;30] The risk of developing inhibitors to FIX is highest after relatively few (10 to 20) exposure days (EDs) to FIX.[23;30;31;32] Often, the allergic reactions occur before inhibitory antibodies are detected.[33] Allergic reactions include pruritus, urticaria, erythema, or angioedema without respiratory or cardiovascular compromise; anaphylactoid syndromes include the above symptoms with respiratory or cardiovascular compromise.

High titer inhibitors require a bypass treatment such as activated prothrombin complex concentrates or activated recombinant factor VII, or temporary removal of the antibody using plasmapheresis or immunoadsorption. An alternative approach is to induce immune tolerance by giving large doses of FIX regularly over several months. However, there are issues with lack of response in patients with an allergic phenotype and the development of nephrotic syndrome following immune tolerance induction (ITI).[25]

The International Society of Thrombosis and Haemostasis-Scientific and Standardization Committee international FIX inhibitor registry was established in 1997 to collect data on the occurrence of inhibitors and the complications associated with them.[16]

Between 1997 and 2006 data from 94 patients were recorded with anaphylaxis reported in 56 of them, and severe allergic reactions in 38. Of 39 patients who underwent some form of ITI only 5 were cleared of inhibitor. Nephrotic syndrome developed in 13 patients 8 to 9 months into the ITI regimen; the patients presented with periorbital edema, proteinuria and hypoalbuminemia. Eleven of the 13 patients had a history of anaphylaxis.

6.3 Population To Be Studied

Previously treated patients (PTPs) with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B, who completed Pivotal Study 250901 or Pediatric Study 251101, and were between 12 and 65 years of age at the time of screening for Study 250901 or < 12 years old at the time of screening for Study 251101, will be recruited in this study (Cohort 1 patients).

In addition, at least 25 BAX326 naïve subjects with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B will be newly enrolled to ensure the evaluation of long-term safey and efficacy in approximately 100 PTPs (Cohort 2 patients).

6.4 Findings from Nonclinical and Clinical Studies

Detailed summaries of nonclinical and clinical findings can be found in the BAX326 Investigator's Brochure.

6.4.1 Phase 1/3 Pivotal Study (250901)

In the pivotal study[v], hemostatic efficacy, pharmacokinetics, safety, and immunogenicity were evaluated in a total of 73 male PTPs aged 12 to 59 years with severe or moderately severe hemophilia B. Subjects with a history of or a detectable FIX inhibitor ≥0.6 BU, a history of severe allergic reactions following exposure to FIX, evidence of severe chronic liver disease (INR >1.4), impaired renal function, a CD4 count <200 cells/mm^3 or any hemostatic defect other than hemophilia B were excluded from participation. The majority of subjects (88%) had arthropathy at screening and target joints (66%).

[v] Full clinical study report finalized on 11 September 2012.

In the randomized, controlled, cross-over PK portion of the study with 28 subjects, PK equivalence of BAX326 and BeneFIX was confirmed, with a 90% CI of 103% to 109% for $AUC_{0\text{-}72\ h}$/dose (and also for $AUC_{0\text{-}72\ h}$) in both the PK Per Protocol Analysis Set (PKPPAS) and the PK Full Analysis Set (PKFAS). The median IR at C_{max} was 0.88 with a range of 0.53-1.35, the mean was 0.87 ± 0.22. The median half-life was 24.58 hours with a range from 15.83 to 52.34 hours and a mean of 26.70±52.34. The PK parameters remained constant at the repeat PK evaluation performed after 6 months of treatment.

The efficacy of BAX326 has been evaluated in the open-label, uncontrolled Part 2 of the study in 73 PTPs. 59 subjects received twice weekly infusions of BAX326 at a dose of 50 IU/kg, ranging from 40-60 IU/kg, which could be increased up to 75 IU/kg. They also received BAX326 for the treatment of bleeds. An additional 14 PTPs received BAX326 for treatment of bleeding episodes only. Of the 59 subjects, 56 subjects received prophylaxis for at least 3 months and were included in the analysis for prophylaxis. The median treatment duration was 6 months (range 5.36 to 9.13). Of these 56 subjects 42.9% (24 subjects) did not experience any bleed. The median annualized bleeding rate (ABR) was 1.99 (range 0-23.4), the median ABR for spontaneous and joint bleeds was 0 (range: 0.0-15.6 and 0.0 – 21.5, respectively). The mean total ABR of historical controls was compared with the mean total ABR resulting from twice-weekly treatment with BAX326. The historical control is based on a meta-analysis of data from 12 studies published from 1976 to 2011 with a total of 276 hemophilia B patients (children and adults) treated on-demand with various factor IX products for a mean duration of 19.6 months. The mean total ABR was 20.0 ± 39.4 (95% CI 15.3; 24.6), whereas the mean total ABR in the prophylactic cohort (based on data of an *interim* analysis with n=56 with at least 3 months treatment) was 4.20 ± 5.75 (95% CI 2.66; 5.74). The difference was statistically significant ($p < 0.001$) with a reduction of total ABR by 79%.

Of the 249 bleeds, 84.7% were controlled with 1-2 infusions (61.4% treated with only 1 infusion). Hemostatic efficacy at resolution of bleed was rated ‘excellent’ or ‘good’ in a total of 96.0% of all treated BEs.

BAX326 was safe and well tolerated in all treated subjects. No subjects developed inhibitors to FIX; no subjects developed total binding antibodies to FIX, CHO proteins or to rFurin considered treatment-related. There were no severe allergic reactions or thrombotic events. Occasional elevated prothrombotic markers pre- and post-infusion in some subjects did not reveal any pattern indicative of thrombogenicity with either BAX326 or BeneFIX, and were not associated with AEs. No significant treatment-related changes in laboratory values or vital signs were recorded.

No deaths or related SAEs occurred and only three non-serious related AEs (n=2, 2.7%) were reported (two of which were mild and related, and one of unknown severity and causality rated 'related').

6.4.2 Phase 3 Surgery Study 251002

Study **251002** was a phase 3, prospective, open-label, uncontrolled, multicenter study designed to evaluate the hemostatic efficacy and safety of BAX326 in approximately 40 subjects with severe or moderately severe hemophilia B undergoing major and minor surgical, dental or other invasive procedures. The full-analysis efficacy set (FAS) comprises 38 surgeries, of which 21 were major and 17 were minor surgeries. The 21 major surgeries comprised 14 orthopedic and 7 non-orthopedic surgeries (3 abdominal, 3 dental, 1 surgical excision of tumor from soft tissue). The 17 minor surgeries comprised 5 orthopedic (4 intra-articular infiltration, 1 synoviorthesis) and 12 non-orthopedic surgeries (11 dental, 1 intra-articular injection).

For patients undergoing major surgeries a PK evaluation had to be performed. All patients were dosed based on their most recent individual IR. Also, depending on the subject's individual PK, infusions had to be repeated every 8 to 24 hours. The recommended initial loading dose of BAX326 was to ensure that during surgery FIX activity levels of 80-100% for major surgeries and 30-60% for minor surgeries were maintained. rFIX was administered by bolus infusion. Hemostasis was maintained throughout the study duration.

The assessment of the hemostatic responses at various timepoints is shown in Table 6.4-1.

Table 6.4-1
Hemostatic Efficacy (Full Analysis Set)

	----------Major Surgeries----------				----------All Surgeries----------			
Efficacy Category	Intraoperative N = 21 n (%)	Drain Removal[a] N = 14 n (%)	Postoperative Day 3[b] N = 7 n (%)	Discharge N = 21 n (%)	Intraoperative N = 38 n (%)	Drain Removal[a] N = 14 n (%)	Postoperative Day 3[b] N = 8 n (%)	Discharge N = 38 n (%)
Excellent	20 (95.2)	10 (71.4)	6 (85.7)	12 (57.1)	37 (97.4)	10 (71.4)	7 (87.5)	29 (76.3)
Good	1 (4.8)	4 (28.6)	1 (14.3)	7 (33.3)	1 (2.6)	4 (28.6)	1 (12.5)	7 (18.4)
Fair	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.3)
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] At time of drain removal, if applicable
[b] At postoperative day 3 for major elective surgery where no drain is employed

Source: Full CSR 251002 Table 12

Six subjects in the FAS, who all underwent major orthopedic surgery, received blood product transfusions, either in the form of packed red blood cells (PRBC) or fresh frozen plasma (FFP) or both. In the FAS, the mean volume transfused was 834.3 (358.7) mL (range: 520-1339 mL) during the intraoperative period (n=6) and 414.0 (227.7) mL (range: 253-575 mL) during the postoperative period (n=2).

Bleeding episodes were reported for two subjects. Both subjects had undergone major orthopedic surgery (knee replacements) and had minor bleeding from the surgical incision. The bleedings occurred 7.9 and 9.9 days after surgery respectively and no hospitalization was required for both subjects.

BAX326 was safe and well tolerated in hemophilia B subjects who received BAX326 for peri-operative management. Only one possibly related AE (hemorrhagic anemia) was reported. This event was resolved at the completion of the study. Otherwise, no thrombogenic events or severe allergic reactions, nor induction of inhibitory antibodies to FIX or total binding antibodies to FIX were observed.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Clinical data with BAX326 have been generated in the completed Phase 1/3 pivotal study (Study 250901), the completed Phase 2/3 study 251101 in pediatric PTPs < 12 years of age and the completed Phase 3 surgery study 251002. Additional data are collected in the present continuation study (Study 251001) to further generate data on efficacy, safety and immunogenicity until subjects have accumulated a total of at least 100 EDs or until the product is licensed in their respective country, however no later than December 31, 2016. A limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs. Subjects who have completed the BAX326 pivotal or BAX326 pediatric study can be transitioned into this study.

BAX326 was shown to be efficacious for routine prophylactic treatment and control of bleeding episodes (on-demand treatment) in PTPs across all age groups with hemophilia B. BAX326 was also found to be efficacious in the surgical hemostasis of 38 surgeries, of which 21 were major (14 major orthopedic surgeries) and 17 were minor surgeries.

A total of 4 clinical studies with a total of 99 unique subjects treated with BAX326 in one or more of the 4 studies have been included in an integrated analysis of safety (ISS) with a data cut-off date of 14 June 2013: 73 subjects treated either prophylactically (n=59) or on-demand (n=14) with BAX326 in the completed pivotal study 250901, 23 subjects treated prophylactically with BAX326 in the completed pediatric study 251101, 30 subjects treated in the surgery study 251002, which was ongoing at the time of the ISS but has in the meantime been completed[vi], as well as available safety data from the ongoing continuation study 251001 (n=82).[vii] The 99 unique subjects in these 4 studies received at least one infusion of BAX326, with a total consumption of 50,756,155 IU of BAX326 in 14,018 infusions. The majority of infusions were administered for prophylaxis (40,172,963 IU administered in 11,504 infusions). Exposure per subject was a median of 156 EDs (range: 8 to 316 exposure days), with a median of 163 infusions per subject (range: 8 to 327 infusions) and a median consumption of BAX326 per subject of 8201.8 IU/kg (range: 376 to 22,705 IU/kg).

Of the 99 treated subjects, 11 unique (11.1%) subjects were <6 years of age, 12 (12.1%) were 6 to <12 years of age, 3 (3.0%) were adolescents (12 to <16 years of age) and 73 (73.7%) were adults (16 years of age and older).The majority (86.9%) of subjects were White, 1.0% was Black or African American, 5.1% were Japanese, 3.0% were Native Latin American, 2.0% were Mestizo, 1.0% was Arabic and 1.0% was Indian.

A total of 337 AEs were reported in 80/99 (80.8%) subjects treated with at least 1 infusion of BAX326. There were no deaths, and no subjects developed inhibitory antibodies to FIX. No subjects developed treatment-related binding antibodies to FIX.[viii] There were no thrombotic events or severe allergic reactions. Only 10 AEs in 8 (8.1%) subjects were considered serious, and all of these were classed by the relevant investigator and sponsor as being unrelated to IP. The majority of AEs was non-serious (327/337) and considered unrelated to IP (321/337). Overall, the majority of the non-serious AEs appear to have been related to mild infections or gastrointestinal disease, abnormal immunology tests (indeterminate antibodies to FIX or rFurin) or arthralgia, a well-described complication of hemophilia, and not related to IP. Two subjects exhibited transiently positive antibodies in the rFurin assay during the Continuation Study with a titer of the lower limit for detection of specificity (1:80). Ten SAEs were reported for 8 (8.1%) subjects. None of the 10 SAEs were judged by the investigator or the sponsor to be possibly or probably related to BAX326.

[vi] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.
[vii] Protocol numbers: 250901 = pivotal, 251001 = continuation, 251002 = surgery, 251101 = pediatric.
[viii] More than 2-dilution step increase in titer compared to pre-study level at screening

Surgery Study 251002 was completed in May 2014.[ix] BAX326 was safe and well tolerated in hemophilia B subjects who received BAX326 for peri-operative management. A total of 581 BAX326 infusions were used for the 38 surgeries (of which 21 were major surgeries) performed in this study. Only one possibly related AE (hemorrhagic anemia) was reported. This event was considered to be unrelated by Baxter and was resolved at the completion of the study. Otherwise, no thrombogenic events or severe allergic reactions, nor induction of inhibitory antibodies to FIX or total binding antibodies to FIX were observed.

Taken together, the safety assessments utilized in the integrated analysis of 2013 and the newly completed surgery study demonstrate safety and tolerability of BAX326 in various clinical settings including perioperative management in subjects with severe or moderately severe hemophilia B.

Preclinical and clinical experience suggest that BAX326 has a comparable safety profile to BeneFIX, and thus, in this Phase 3 study, the anticipated risk profile of BAX326 is expected to remain similar to that of BeneFIX. The BeneFIX SPC [3] describes the following adverse events (AEs) observed in clinical studies and which have also been reported for other (plasma-derived) FIX concentrates:

Uncommon (occurrence ≥ 1/1,000 to ≤ 1/100): Dizziness, headache, altered taste, lightheadedness, nausea, cellulitis, phlebitis, injection site reactions, injection site discomfort and neutralizing antibodies.

Rare (occurrence ≥ 1/10,000 to ≤ 1/1,000): Vomiting, pyrexia, hypersensitivity/allergic reactions: such reactions may include anaphylaxis, bronchospasm/respiratory distress (dyspnea), hypotension, angioedema, tachycardia, chest tightness, urticaria, hives, rash, burning sensation in jaw and skull, chills (rigors), tingling, flushing, lethargy, restlessness, dry cough/sneezing, blurred vision. Although BeneFIX only contains FIX, the risk of thrombosis and disseminated intravascular coagulation (DIC) is recognized. Patients with liver disease, neonates, patients at risk for thrombotic phenomena or DIC or who have undergone surgery should be closely followed for thrombotic markers. There have been post-marketing reports of thrombotic events, including life-threatening superior vena cava syndrome in critically ill neonates while receiving a continuous infusion with BeneFIX.

[ix] Surgery Study 250112: Last subject out 2014 May 15, final CSR version date 2014 Oct 14.

Inadequate therapeutic response and inadequate FIX recovery have been reported during the post-marketing use of BeneFIX.

For additional information, please refer to the BAX326 Investigator's Brochure.

In this Phase 3 clinical study, subjects will continue receiving BAX326 for a period of up to approximately 48 months to further evaluate the hemostatic efficacy in the prevention and treatment of bleeding episodes as well as the safety of BAX326. Subjects will receive BAX326 until the product is licensed in their respective countries or until they accumulate a total of 100 EDs to BAX326, including the EDs from BAX326 Pivotal Protocol 250901, or Protocol 251101 for pediatric subjects, whichever occurs last. In addition to standard and modified prophylaxis and on-demand treatment (Section 8.6.3), the hemostatic efficacy and safety of a PK-tailored, prophylactic treatment regimen will be evaluated (Section 8.6.3.1.1).

Therefore, any individual patient may benefit from an anticipated safe and efficacious treatment with BAX326 over a prolonged period of time.

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this BAX326 Continuation Study is to further investigate the safety, hemostatic efficacy, and immunogenicity of BAX326, and changes in HR QoL of BAX326 in PTPs with severe and moderately severe hemophilia B who completed either BAX326 Pivotal Study 250901 or BAX326 Pediatric Study 251101 (Cohort 1) as well as in approximately 25 BAX326 naïve subjects (Cohort 2), until BAX326 is licensed in the subject's country or until the accumulation of up to approximately 100 EDs of treatment with BAX326, whichever occurs last, however no later than December 31, 2016. A limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs.

7.2 Study Objectives

The objectives of this study are to:

- Further evaluate safety of BAX326 in terms of IP-related AEs as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs
- Further evaluate the hemostatic efficacy of BAX326 in the prevention and routine prophylaxis of acute bleeding episodes using various dose regimens
- Further evaluate the hemostatic efficacy of BAX326 in the management of acute bleeding episodes
- Further evaluate the immunogenicity of BAX326 for up to 100 EDs to BAX326[x]
- Monitor IR of BAX326 over time
- Evaluate changes in health-related quality of life (HR QoL), Patient Activity Level and health resource use
- Exploratory: To correlate pre-infusion TGA parameters with pre-infusion FIX levels and spontaneous breakthrough bleeds in a subset of subjects receiving twice weekly standard or modified prophylaxis including PK tailored prophylaxis.

[x] Subjects who have participated in BAX326 Pivotal Study 250901 or Pediatric Study 251101, and in BAX326 Continuation Study 251001 will have accumulated a total of up to approximately 100 EDs in both studies.

8. STUDY DESIGN

8.1 Overall Study Design

This continuation study is a prospective, open-label, multicenter, uncontrolled, phase 3 study in approximately 100 PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B, who have completed either the pivotal Phase 1/3 BAX326 protocol 250901 or the pediatric protocol 251101 (Cohort 1) as well as in approximately 25 BAX326 naïve subjects (Cohort 2).

Any subject requiring elective or emergency surgery may be temporarily transitioned to the BAX326 Surgery Study (# 251002) [xi] for peri- and postoperative hemostatic management. Exemptions may be granted for minor interventions. As soon as the subject is discharged from the (surgical) study site, he will be switched back to this continuation study until completion. Please note that for subjects switching back to this study from the surgery study, the respective visit window may be extended from ± 1 week to ± 2 weeks. Outside this window, an additional end-of-study visit for the surgery study must be arranged.[xi] Once the surgery study is completed, all surgeries for subjects must be approved by the sponsor. If not approved, the subject will be withdrawn from further study participation.

8.1.1 Subjects Transitioning from BAX326 Pivotal or BAX326 Pediatric Study

All subjects who completed Baxter Pivotal Study 250901 or Pediatric Study 251101 have an option to enroll in the continuation study (Cohort 1).[xii] The treatment regimen with BAX326 will be at the discretion of the investigator and will consist of one of the following treatment options:

- Standard prophylaxis with twice weekly prophylactic infusions of 50 IU/kg (range of 40-60 IU/kg, which may be increased to 75 IU/kg, in subjects ≥ 12 years of age; range of 40-80 IU/kg in pediatric subjects < 12 years), or
- modified prophylaxis determined by the investigator. The dose can be increased up to 100 IU/kg, if applicable;or
- PK-tailored prophylaxis based on subject's individual PK. The maximum dose is 120 IU/kg; or
- on-demand treatment

[xi] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.
[xii] The continuation study started after the first subject had completed Pivotal Study 250901.

The screening visit for the continuation study will be performed on the same day as the end of study/termination visit of the pivotal or pediatric study in order to ensure continuity of BAX326 therapy. Subjects can be given the Informed Consent Form prior to the termination visit of Pivotal Study 250901 or Pediatric Study 251101 to ensure ample time for reviewing and considering the participation in the continuation study 251001. Subjects will be supplied with IP for a maximum of 5 weeks at the screening visit. The subject will then return to the study site no later than 4 ± 1 weeks to review the results of the screening visit (including results from termination visits for Study 250901 or 251101), and confirm their eligibility for continued participation. At Week 4 ± 1 following the screening visit at the very latest, the subject will return to the study site.

Subsequent study visits will be performed every 3 months[xiii] ± 1week after study start (ie, screening visit) until study completion; additional visits may occur if clinically indicated. Hemostatic efficacy and the occurrence of AEs will be evaluated based on the review of the patient diary. Testing for IR, inhibitory and binding antibodies, clinical chemistry and hematology will be performed at the same time points. In addition to the time points mentioned above, the presence of inhibitory and total binding antibodies to FIX will be tested whenever clinically indicated, e.g. on lack of response to treatment, or if severe allergic reactions occur, such as anaphylaxis.

At the same time points health resource use will also be determined. Every other visit (ie, every 6 months ± 1 week), data on HR QoL will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject or subject's legal representative or by authorized study site personnel in the patient diary: bleeding location, type, severity, onset date and time, infusion date and time, analgesics required, and clinical efficacy according to the rating scale.

8.1.2 Newly Recruited Subjects

At least 25 subjects who have not previously been exposed to BAX326 will be enrolled (Cohort 2). Once eligibility criteria are confirmed, subjects will receive prophylactic treatment over a period of up to approximately 100 EDs to BAX326, or until BAX326 is approved in the subject's country, whichever occurs last, but no later than December 31, 2016. A limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs.

[xiii] 1 month calculated on a 30-day basis

The treatment regimen with BAX326 will be at the discretion of the investigator and will consist of one of the following treatment options:

- Standard prophylaxis with twice weekly prophylactic infusions of 50 IU/kg (range of 40-60 IU/kg, which may be increased to 75 IU/kg, in subjects ≥ 12 years of age; range of 40-80 IU/kg in pediatric subjects < 12 years), or
- modified prophylaxis determined by the investigator. The dose can be increased up to 100 IU/kg, if applicable; or
- PK-tailored prophylaxis. The maximum dose is 120 IU/kg.[34]

Hemostatic efficacy, safety, and immunogenicity assessments will be performed at Week 4 ± 1, Month 3 ± 1 week and thereafter every 3 months ± 1 week (see Section 8.1.1). IR will be determined at the same time points. An additional inhibitor test will be performed immediately before the first exposure to BAX326, as well as an IR during the first infusion of BAX326. The subject will be monitored for vital signs and the occurrence of AEs. Subjects receiving PK-tailored prophylaxis will follow the schedule as described in Section 8.1.3.

8.1.3 Subjects Receiving PK-Tailored Prophylaxis

Subjects who will receive a PK-tailored dose regimen will undergo an abbreviated PK study with 1 pre- and 5 post-infusion sampling timepoints up to 72 hours following the infusion of 75 ± 5 IU/kg BAX326 to determine FIX activity levels (ie, within 30 minutes pre-infusion, and 30 ± 5 minutes, 9±3 h, 24±6 h, 48±6 h and 72[-6] h post-infusion). Also, blood samples for the determination of TGA parameters will be taken at the same time points. Based on the subject's individual PK, the dose and frequency will be determined to ensure that FIX activity levels in plasma of at least 1% above the subject's individual FIX level observed at baseline are maintained. The maximum dose is 120 IU/kg. Doses higher than 120 IU/kg are not allowed and therefore frequencies requiring a higher dose are excluded.[34] Subjects continuing from the continuation study and newly recruited subjects with confirmed eligibility will receive BAX326 at a dose regimen as determined by the investigator until the dose and frequency, calculated by the sponsor, are available at the study site. Upon availability of the PK-tailored treatment regimen, the subject will start the PK-tailored treatment 4 weeks ±1 prior to the respective next 3-monthly visit. Bleeding episodes will also be treated with BAX326.

Hemostatic efficacy assessments will be performed at the respective next 3 monthly visit after start of the PK-tailored treatment regimen as well as at any subsequent 3 monthly visit. At these same time points, pre- and post-infusion FIX activity levels as well as pre- and post-infusion TGA parameters, if applicable, will be determined to evaluate the potential correlation between pre-infusion FIX levels, TGA parameters and the occurrence of bleeding episodes. In newly recruited subjects, immediately prior to the first infusion of BAX326 a blood sample for FIX inhibitor determination will be drawn.The study site will call the subjects after 8±1, 17 ±1 and 22±1 weeks of start of treatment to discuss the potential occurrence of bleeding episodes and/or AEs.

8.1.4 Additional Blood Sampling for Determination of FIX Activity and TGA Parameters

Additonal blood sampling for FIX activity and TGA determination will be performed in approximately 40 subjects ≥ 12 years of age **without requiring a wash-out period** (see Section 11.1 and Section 11.2 for further details)**.**

In approximately 20 subjects receiving twice weekly standard prophylactic infusions of BAX326, pre- and post-infusion TGA parameters concurrent with IR for FIX will be determined over 6 months at their regular 3-monthly visit. Also, at 4 additional different time points within this 6-month period, pre- and post-infusion TGA parameters and FIX activity level will be determined. On 2 occasions these should be assessed 3 days after a prophylactic infusion of BAX326 (ie, before and after the subsequent prophylactic infusion of BAX326), and on the other 2 occasions 4 days after a prophylactic infusion of BAX326 (ie, before and after the subsequent prophylactic infusion of BAX326 (Table 11.1-4).

For subjects receiving modified prophylaxis, FIX acitivity levels and TGA parameters will also be determined within a 6-month period pre- and post-infusion at 4 different timepoints. The pre- and post-infusion blood draws should occur such that they reflect the dosing interval.

8.2 Duration of Study Period(s) and Subject Participation

The total period of study participation per study subject will vary and can be up to a maximum of 68 months, depending on the date of subject enrollment and the product licensure in the subject´s respective country, and whether the subject has accumulated a total of 100 EDs to BAX326 during the course of the Pivotal (# 250901) or Pediatric (# 251101) Study and the Continuation Study (# 251001), whichever occurs last, but will not last beyond December 31, 2016.

For newly recruited subjects, the study participation will be up to approximately100 EDs, but not beyond December 31, 2016. However, a limited number of patients may not have reached 100 EDs by that date and they will continue until they have reached approximately 100 EDs.

Subjects will participate in this continuation study until BAX326 is licensed in their respective countries, and they have accumulated a total of at least 100 EDs to BAX326, however, no later than December 31, 2016.

The duration of the study will be approximately 68 months depending on the date of licensure in subjects' countries.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

- Adverse events possibly or probably related to IP

8.3.2 Secondary Outcome Measures

8.3.2.1 Hemostatic Efficacy

- Treatment of bleeding episodes:
  - Number of infusions per bleeding episode
  - Overall hemostatic efficacy rating at resolution of bleed
- Prophylaxis: annualized bleeding rate (ABR)
- Consumption of BAX326:
  - Number of infusions and weight-adjusted consumption per month and per year
  - Weight-adjusted consumption per event (for prophylaxis and on-demand)

8.3.2.2 Safety and Immunogenicity

- Development of inhibitory and total binding antibodies to FIX
- Development of antibodies to CHO proteins and rFurin
- Occurrence of severe allergic reactions, e.g. anaphylaxis
- Occurrence of thrombotic events
- Clinically significant changes in routine laboratory parameters (hematology and clinical chemistry), and vital signs

8.3.2.3 Pharmacokinetics

- IR over time
- AUC0-∞ (area under the plasma concentration time curve from time 0 to infinity), IR, T1/2 (elimination phase half-life), MRT (mean residence time), CL (clearance), Vss (Volume of distribution at steady state) [xiv]

8.3.2.4 Health related Quality of Life, Patient Activity Level and Health Resource Use

Outcome measures for health resource use and HR QoL scores are as follows:

- For subjects who are 2 to 7 years of age (at the time of screening for Pediatric Study 251101 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects)[xv]:
  - Generic: PedsQL™ (Parent-proxy versions: age group 2-4 years and age group 5-7 years)
  - Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)
  - Patient Activity Level
- For subjects who are 8 to 11 years of age (at the time of screening for Pediatric Study 251101 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects)[xv]:
  - Disease-specific: Haemo-QoL, short version
  - Generic: PedsQL™ Child version
  - Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)
  - Patient Activity Level

[xiv] If subject receives a PK-tailored dose regimen and did not participate in the PK portion of the BAX326 pivotal or BAX326 surgery study.

[xv] Due to the unavailability of linguistically validated translations of certain HRQoL measures in certain countries, some of these questionnaires may not be administered in all countries participating in this study.

- For subjects who are 12 to 16 years of age (at the time of screening for Pivotal Study 250901 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects):
  - Disease-specific: Haemo-QoL short version
  - Generic: PedsQL™
  - Health utility: EQ-5D
  - General pain assessment through a VAS
  - Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)
  - Patient Activity Level
- For subjects aged 17 years and older (at the time of screening for Pivotal Study 250901 for Cohort 1 subjects or at the time of screening for Study 251001 for Cohort 2 subjects):
  - Disease-specific: Haem-A-QoL
  - Generic: SF-36
  - Health Utility: EQ-5D
  - General pain assessment through a VAS
  - Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)
  - Patient Activity Level

8.3.2.5 Exploratory Outcome Measures

- If applicable, TGA parameters over 72 hours during PK (lag time, time to peak thrombin generation, peak thrombin generation, endogenous thrombin potential [ETP])
- TGA parameters pre- and post-infusion concurrent with IR determination for FIX activity in a subset of subjects receiving twice-weekly standard or modified prophylaxis including PK-tailored prophylaxis with BAX326 as well as at some selected timepoints during prophylactic treatment

8.4 Randomization and Blinding

This section is not applicable.

8.5 Study Stopping Rules

The safety of BAX326 in this study is monitored by an independent Data Monitoring Committee (DMC) on a regular basis as scheduled until the end of 2015. From the beginning of 2016 onwards, the DMC chair will not continue to review all SAEs as sufficient positive safety data from pre- and post-marketing BAX326 exposures are already available.

This study will be halted, pending further review by the sponsor, or stopped under the following circumstances:

- If two or more subjects develop a high titer inhibitory antibody > 5 Bethesda Units (BU) confirmed by the central laboratory, or if two or more subjects develop anaphylaxis following exposure to BAX326 in studies BAX326 Pivotal 250901, BAX326 Pediatric 251101, and BAX326 Continuation 251001, the transition to BAX326 Continuation will be halted. Within 2 weeks of receipt of the second report, Baxalta may decide to halt the study.
- The study may be stopped following any of the planned interim safety reviews or at any time by the sponsor in case of unacceptable risks to subjects, in particular in case of inhibitor development, thrombotic events, or anaphylaxis.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, Reconstitution, Storage, and Shelf-life

BAX326 is formulated as a sterile, nonpyrogenic, lyophilized powder of concentrated rFIX for intravenous injection and is provided in a single-dose vial labeled with the rFIX activity expressed in IU.

The clinical trial material employed for the study will be manufactured in Orth, Austria (BDS) and filled in Thousand Oaks, US (FDP).

BAX326 is infused intravenously after reconstitution with Sterile Water for Injection (SWFI). A single package contains: one vial of lyophilized powder with a nominal potency of 250, 500, 1000, 2000 or 3000 IU/vial; one vial with 5 mL of SWFI; and a needleless transfer device for reconstitution (BAXJECT II). The ancillary package contains: 10, 20, and 30 mL plastic syringes, and a 23-gauge winged infusion set.

Each vial will be labeled with the actual potency in International Units and an Investigational Product Label. The Investigational Product Label will meet country-specific regulatory label requirements.

For reconstitution instructions, please refer to the BAX326 Investigator's Brochure.

Please note: For an individual subject, study product from only one lot/infusion with a nominal potency of 500 IU/vial may be used for IR and abbreviated PK assessment.

Vials from different lots/infusion, preferably not more than two different lots/infusion may be used for the prophylactic or on-demand treatment, however each vial must be reconstituted with its own kit, ie, a separate BAXJECT II must be used for reconstitution of each vial.

BAX326 is to be stored at +2° to +8°C (36 to 46°F). Freezing should be avoided to prevent damage to the diluent vial. The reconstituted product should be used immediately, but no longer than 3 hours after reconstitution. Chemical and physical in-use stability has been demonstrated for 3 hours at temperatures up to 25°C. Additional shelf-life information can be found in the BAX326 Investigator's Brochure.

8.6.2 Administration

Following reconstitution, BAX326 should be administered at room temperature and within 3 hours of reconstitution. Plastic syringes provided by the sponsor must be used with this product since proteins such as BAX326 tend to stick to the surface of glass syringes. The infusions will be administered by intravenous bolus at a maximum infusion rate of 10 mL/minute. The investigator/ subject shall ensure that no visible residual volume remains in the vial and that the complete content is administered. Partial (ie, not whole) vials may be used in minor subjects < 12 years of age for IR or PK determination as described in Section 8.6.3.1.1 or for other infusions for subjects not older than 5 years of age only upon agreement with Baxalta.

8.6.3 Description of Treatment

All subjects will receive exclusively BAX326.

The treatment with BAX326 will be at the discretion of the investigator and will consist of either prophylaxis or on-demand. Newly recruited subjects will receive prophylactic treatment only.

8.6.3.1 Prophylactic Treatment

The prophylactic treatment regimen with BAX326 will be at the discretion of the investigator and will consist of one of the following treatment options:

- Standard prophylaxis with twice weekly prophylactic infusions of 50 IU/kg (range of 40-60 IU/kg, which may be increased to 75 IU/kg, in subjects ≥ 12 years of age; range of 40-80 IU/kg in pediatric subjects < 12 years), or
- modified prophylaxis determined by the investigator. The dose can be increased up to 100 IU/kg, if applicable; or
- PK-tailored prophylaxis based on subject's individual PK. The maximum dose is 120 IU/kg.[34]

Please note:

The dose and dosing frequency should be adjusted according to the individual subject's age, the number of breakthrough bleeds and/or the subject's physical activity.

It is recommended to administer prophylactic infusions prior to weekdays with increased physical activity.

In subjects with severe hemophilic arthropathy and/or target joints who continue experiencing recurrent bleeding episodes despite adjustments of the prophylactic dose and/or dosing frequency, an ultrasound of the affected joint(s) should be performed to verify the presence of a bleed.

Dose and/or frequency adjustments should be performed if a subject meets either of the following criteria:

- **Two or more spontaneous** (not related to trauma) bleeding episodes in the same target joint within any 3-month period, **OR**
- **One or more spontaneous** (not related to trauma) bleeding episodes in a non-target joint or a non-joint within any 3-month period

In such a case, the dose and/or frequency will be increased. The dose is not to exceed 100 IU/kg and an increase in frequency should be considered. It is recommended to consult the sponsor.

The regimen should preferably be maintained until the end of the study, unless clinical circumstances or the subject's wish necessitate a change as described above. Any change in the regimen, and the reason for such change, will be recorded in the eCRFs.

8.6.3.1.1 PK-Tailored Prophylaxis

Subjects receiving PK-tailored prophylactic treatment who have not participated in a PK study either in the BAX326 pivotal or BAX326 surgery study will undergo an abbreviated PK study with 1 pre- and 5 post-infusion sampling timepoints up to 72 hours following the infusion of 75±5 IU/kg of BAX326. Only 500 IU potency vials from one lot may be used for the PK study in individual subjects. The actual vial potency will be used to calculate the total units administered and rounded up or down to the nearest whole vial. In subjects < 12 years of age, the total calculated dose may not be rounded up or down to the nearest whole vial. There must be a minimum wash-out period of 5 days, preferably 7 days, prior to the PK infusion and the subject must be in a non-bleeding state. Based on the subject's individual PK, the dose will be calculated to ensure that FIX activity levels in plasma of at least 1% above the subject's individual FIX level observed at baseline are maintained. The maximum dose is 120 IU/kg. Doses higher than 120 IU/kg are not allowed and therefore frequencies requiring a higher dose are excluded.[34] Subjects continuing from the continuation study and newly recruited subjects with confirmed eligibility will receive BAX326 at a dose regimen as determined by the investigator until the dose and frequency, calculated by the sponsor, are available at the study site. Bleeding episodes will also be treated with BAX326.

8.6.3.2 Treatment of Bleeding Episodes

Bleeding episodes will be treated with BAX326. Once the bleed has stopped, the subject should resume the established treatment regimen, if applicable. The following guidance may be employed when determining the dose for treatment of bleeding episodes [3;35]: The FIX level should not fall below the given plasma activity level in the corresponding period (see Table 8.6-1).

Table 8.6-1
Dose for treatment of bleeding episodes

Degree of hemorrhage	FIX level required (%) (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
Early hemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 24 hours. Duration: at least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleeding or hematoma	30-60	Repeat infusion every 24 hours for 3-4 days or more until pain and acute disability are resolved.
Life threatening hemorrhages	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.

In subjects ≥ 12 years of age, the required units will be calculated according to the following formula:

body weight (kg) x desired FIX rise (%) (IU/dL) x {reciprocal of observed recovery}

Given an anticipated recovery of 0.9 [IU/dl]/[IU/kg], the required units are calculated using the following formula:

body weight (kg) x desired FIX rise (%or (IU/dL) x 1.1 IU/kg

In subjects < 12 years of age, the required units will be calculated according to the following formula:

body weight (kg) x desired FIX rise (%) (IU/dL) x {reciprocal of observed recovery}

Given an anticipated recovery of 0.7 [IU/dl]/[IU/kg], the required units are calculated using the following formula:

body weight (kg) x desired FIX rise (%or (IU/dL) x 1.4 IU/kg

Given the wide range of individual recoveries, it is critical to adjust the dose once the IR becomes available after initial PK assessment and subsequent IR determinations.

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. It is rare that FIX products require more than once daily administration. However, certain underlying clinical conditions and/or the severity of the bleed may warrant an adjustment from these recommendations. In such a case, the reasons and need for changing the treatment approach should be recorded in the "General Comments" section of the eCRF. Additional infusions may be given to maintain hemostasis and until bleed-related symptoms have resolved.

It is important to clearly indicate after which infusion the bleed stopped and whether additional infusions are given to maintain hemostasis. This generally does not coincide with the cessation of objective signs of bleeding, such as pain or swelling, since the absorption of blood would still be ongoing. Particularly in the case of severe hemophilic arthropathy and/or previous joint surgery combined with severe bleeds, it is more difficult to define exactly the time point of the cessation of the bleed.

It is also recommended to verify the presence of a joint bleed by ultrasound if despite several infusions of BAX326 the pain persists.

Note: The actual vial potency will always be used to calculate the total units administered and rounded up or down to the nearest whole vial for all BAX326 administrations for prevention and treatment of bleeding episodes.

8.6.3.3 Surgery

Subjects requiring elective or emergency surgery may be temporarily transitioned to the BAX326 surgery study for their peri- and postoperative hemostatic management. The surgery study is described in a separate protocol (# 251002). As soon as they are discharged from the (surgical) study site , they will be switched back to this continuation study until completion. Exemptions may be granted for minor interventions in case the surgery study is not in place at a study site or if the surgery study is completed globally.[xvi]

8.7 Investigational Product Accountability

The investigator will ensure that the IP is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g. infusion center; home, as applicable per study design). Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

[xvi] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or questionnaires completed by the subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and CRFs, see Section 18.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

9.1.1 Subjects Transitioning From Baxter Pivotal Study 250901 or Pediatric Study 251101 (Cohort 1)

Subjects who have completed Baxter Pivotal Study 250901 or Pediatric Study 251101 and meet **ALL** of the following criteria are eligible for this study:

- Subject and/or legal representative has/have voluntarily provided signed informed consent.
- Subject has completed Baxter Pivotal Study 250901 or Pediatric Study 251101.
- Subject has not developed an inhibitory FIX antibody during Baxter Pivotal Study 250901 or Pediatric Study 251101.
- Subject is human immunodeficiency (HIV) negative or is HIV+ with a viral load < 200 particles/μL ~ < 400,000 copies/mL.
- Subject is immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm^3.
- If female of childbearing potential, subject presents with a negative pregnancy test and agrees to continue employing adequate birth control measures for the duration of the study.
- Subject is willing and able to comply with the requirements of the protocol.

9.1.2 Newly Recruited Subjects (Cohort 2)

Newly recruited subjects who meet **ALL** of the following criteria are eligible for this study:

- Subject and/or legal representative has/have provided signed informed consent.
- Subject is 2 to 70 years old at the time of screening.
- Subject is naïve to BAX326
- Subject has severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B (based on the one stage activated partial thromboplastin time (aPTT) assay), as tested at screening at the central laboratory.
- Subject aged ≥ 6 years has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 150 EDs
- Subject aged < 6 years has been previously treated with plasma-derived and/or recombinant FIX concentrate(s) for a minimum of 50 EDs.
- Subject has no evidence of a history of FIX inhibitors.

- Subject is immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm^3 at screening.
- Subject is human immunodeficiency (HIV) negative or is HIV+ with a viral load < 200 particles/μL ~ < 400,000 copies/mL
- If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
- Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

9.2.1 Subjects Transitioning from Pivotal Study 250901 or Pediatric Study 251101 (Cohort 1)

Subjects who have completed Baxter Pivotal Study 250901 or Pediatric Study 251101 and meet **ANY** of the following criteria are not eligible for this study:

- Subject received factor IX product(s) other than BAX326 upon completion of Baxter Pivotal Study 250901 or Pediatric Study 251101.
- Subject has been diagnosed with an acquired hemostatic defect other than hemophilia B.
- For subjects transferring from Pivotal Study 250901: The subject's weight is < 35 kg or > 120 kg.
- Subject's platelet count is < 100,000/mL.
- Subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).
- Subject has active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 5 times the upper limit of normal.
- Subject is scheduled to receive during the course of the study, an immunomodulating drug (e.g. corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
- Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.

- Subject is planned to take part in any other clinical study, with the exception of BAX326 Surgery Study[xvii] as described in this protocol, during the course of the Continuation Study.
- Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

9.2.2 Newly Recruited Subjects (Cohort 2)

Newly recruited subjects who meet ANY of the following criteria are not eligible for this study:

- Subject has a history of FIX inhibitors with a titer ≥ 0.6 Bethesda Units (BU) (as determined by the Nijmegen modification of the Bethesda assay or the assay employed in the respective local laboratory) at any time prior to screening.
- Subject has a detectable FIX inhibitor at screening, with a titer ≥ 0.6 BU as determined by the Nijmegen modification of the Bethesda assay in the central laboratory.
- Subjects ≥ 12 years of age: Subject's weight is < 35 kg or > 120 kg
- Subject has a history of allergic reaction, eg, anaphylaxis, following exposure to FIX concentrate(s).
- Subject has a known hypersensitivity to hamster proteins or rFurin.
- Subject has evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
- Subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal).
- Subject has severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4 hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly and history of esophageal varices.
- Subject has active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 5 times the upper limit of normal.

[xvii] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia B.
- Subject's platelet count is < 100,000/mL.
- Subject has a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance.
- Subject is currently receiving, or is scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than anti-retroviral chemotherapy.
- Subject has participated in another investigational study within 30 days of enrollment.
- Subject is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees of the investigator or site personnel conducting the study.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the Completion/Termination eCRF. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) are described in Section 10.6 and Section 21.2. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject, or if the subject does not meet the eligibility criteria but was inadvertently enrolled in the study.

Subjects will also be discontinued from further study participation for the following reasons:

- The subject has developed an inhibitor to FIX ≥ 0.6 BU confirmed at the central laboratory.

- The subject with chronic hepatitis B or C has developed ALT/AST levels exceeding 5 times the upper limit of normal which may be confirmed by repeating the test.
- The subject has developed clinical signs of a thrombotic event.
- The subject has experienced severe allergic reaction(s), e.g. anaphylaxis, upon exposure to BAX326.
- The subject has received an immunomodulating drug (eg, α-interferon, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day) other than anti-retroviral chemotherapy during the course of the study.
- The subject requires major surgery which will be performed outside the scope of the surgery study (e.g site not participating in surgery study, surgery study completed[xviii])
- The subject becomes pregnant (if the subject is female of childbearing potential, which is not likely in this study). IP exposure will be discontinued. Attempts will be made to follow her through completion of the pregnancy. The investigator will record a narrative description of the course of the pregnancy and its outcome.
- The subject begins lactating (if the subject is female of childbearing potential, which is not likely in this study). IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.

Any subject who develops inhibitors or anaphylaxis, or demonstrates clinical signs of a thrombotic event, will be further followed up and treated according to best clinical practice.

[xviii] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the Subject Identification Code (SIC): protocol number (ie, 251001) to be provided by the sponsor, 2-digit number study site number (e.g., 02) to be provided by the sponsor, and 4-digit subject number (e.g., 0003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 251001-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birthdate would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log will also serve to document the reason for a screening failure.

A detailed breakdown of the study procedures is shown in Supplement 21.1 "Flow Diagram of Study Procedures". Details on the procedures and assessments to be performed at each study visit, including screening, can be found in Supplement 21.1 "Schedule of Study Procedures and Assessments" and Supplements 21.3 "Clinical Laboratory Assessments for Transition Subjects" and 21.4 "Clinical Laboratory Assessments for Newly Recruited Subjects".

Blood sampling and laboratory analyses can be repeated if the primary sample has been lost or damaged. All screening data will be collected and reported in eCRFs, regardless of screening outcome. For the purpose of analysis, only the data from the latest retest will be used.

Subjects should not be actively bleeding at the time of screening and at the scheduled study visits.

The following provisions apply for subjects who are enrolled in parallel in the BAX326 Surgery Study (Protocol 251002) [xix]:

Once a subject has signed informed consent for the BAX326 surgery study, s/he continues receiving treatment with IP as part of this BAX326 continuation study until the start of surgery. If a regular study visit has taken place within 4 weeks of the screening visit for the surgery study, the safety laboratory data from the current study can be used. Similarly, if a regular study visit is planned for this study, and the surgery study's completion/termination visit falls within a ± 2-week window of this visit, then the results from this study will be used for the completion/termination visit of the surgery study.

10.3.1 Subjects Transitioning from BAX326 Pivotal or BAX326 Pediatric Study (Cohort 1)

The screening visit will be performed on the same day as the completion/ termination visit for the 250901 (pivotal) or 251101 (pediatric) protocol.[xx] The Informed Consent will be obtained before any procedures related to the BAX326 Continuation study are performed. Tests performed for the BAX326 completion/ termination visit of the main study will not be repeated for screening in Study 251001, and the relevant data obtained for the 250901 or 251101 completion/termination visit will be transcribed to the screening visit eCRF.

Following the screening visit, subjects will continue receiving BAX326 until his/her eligibility for the study is confirmed. If the eligibility criteria are not met, a completion/termination visit will be performed at the Week 4±1 visit following screening.

10.3.2 Newly Recruited Subjects (Cohort 2)

All screening/baseline evaluations must be completed within 42 days or repeated if more than 42 days have elapsed. Exemptions may be granted for administrative reasons by the sponsor, eg, delay in availability of laboratory results. For the purpose of analysis, only the data from the most recent screening visit will be used. If a subject does not satisfy all screening criteria, the same subject may be re-screened at a later date. A complete or partial re-screen may also become necessary at the discretion of the investigator or sponsor. All screening data will be collected and reported in eCRFs, regardless of screening outcome.

[xix] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

[xx] Pivotal Study 250901and Pediatric Study 251101 have been completed (Last Subject Out: 03 May 2012 [Pivotal] and 14 May 2013 [Pediatric]).

Subjects should not be actively bleeding at the time of screening and at the scheduled study visits, and a wash-out period of at least 5 days, preferably 7 days, should be observed.

10.4 Medications and Non-Drug Therapies

The following medications are **not** permitted during the course of the study:

- Any FIX concentrate other than BAX326
- Immunomodulating drugs other than anti-retroviral chemotherapy (e.g. α-interferon, or corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day)

A subject who has taken any of these medications will be discontinued from the study.

10.5 Subject Diary

A subject diary will be provided to each subject or the subject's legally authorized representative:

- At screening/at all the following study visits, ie, every 3 months ± 1 week, except the study completion/termination visit

The subject diary will be used to record the following information:

- Infusion record of IP (date, time of the infusion, number of units infused, number of vials utilized, lot number, and reason for infusion [bleeding episode, or prophylactic infusion])
- Details of bleeding episodes (site, type, and severity of bleeding) and response to treatment as described in Section 11.3 "Hemostatic Efficacy"
- All AEs will be recorded that do not fall within the provisions of Section 12.3 "Untoward Medical Occurrences Not Considered Adverse Events".
- Concomitant medications taken (including immunizations) and non-drug therapy
- Drug accountability (number of unused vials of IP remaining in the subject's refrigerator will be recorded, prior to each study visit).

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be returned to the investigator at interval study visits and will serve as source documentation. At each interval study visit as described above, the subject will turn in a single diary and receive a blank one. The subject diary will serve as a source record and remain at the study site. The currently used paper diary may be replaced by an electronic diary.

Note:

It is crucial that the investigator evaluates and discusses with the subject at each study visit whether the subject adheres to the prescribed treatment regimen for prevention, if applicable, and treatment of bleeding episodes, and whether the subject has correctly entered all necessary information. The investigator will review the diary for completeness, ask for missing information, and enter the examined data on the eCRFs. Any unclear or implausible information should be immediately clarified with the subject at each study visit and instructions related to treatment and data entry be reinforced.

The investigator will review the AE and concomitant medication record, the number of infusions used to treat bleeding episodes and the corresponding efficacy rating and discuss it with the subject, and enter the information on the appropriate eCRF. For example, if a subject writes in the diary that he or she has taken paracetamol but no AEs are entered, the investigator should ensure that the corresponding condition (eg, headache) is also recorded.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, followed the protocol. Reasons for completion/discontinuation will be reported on the Completion/Termination eCRF, including:

- Completed
- Eligibility criteria not met
- Screen failure
- AE
- Discontinuation by subject (eg, withdrawal of Informed Consent, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout)
- Physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery)
- Study terminated by sponsor
- Any reason as specified in Section 9.3 “Withdrawal and Discontinuation”
- Or other (reason to be specified by the investigator, eg, technical problems)

Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate eCRF. Refer to Section 9.3 for reasons for premature discontinuation or withdrawal.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) can be found in Supplement 21.2 Schedule of Study Procedures and Assessments and Supplements 21.3 (Clinical Laboratory Assessments for Transition Subjects) and 21.4 (Clinical Laboratory Assessments for Newly Recruited Subjects). The reason for discontinuation will be recorded on the eCRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. All unused IP provided to the subject will be returned to the study site.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the treatment regimen and study visits will be monitored by direct review of the subject's source data at the sites and evaluated against the protocol requirements. Additionally, electronic edit checks will be performed on all protocol-specified treatment data that is collected to ensure the quality and accuracy of the data.

11. ASSESSMENT OF EFFICACY

11.1 Determination of FIX Activity

For the determination of IR and PK at regular study visits, as described in the sections below, the following procedure should be followed:

Subjects will be infused with 75 ± 5 IU/kg of BAX326. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. For the determination of FIX activity, only vials of 500 IU potency from one lot/infusion should be used.

The actual vial potency will be used to calculate the total units administered.

Note:

- **In subjects ≥ 12 years of age, vials should be rounded up or down to the nearest whole vial.**
- **In subjects < 12 years of age, the total calculated dose should not be rounded up or down to the nearest whole vial in case a dose of75 ± 5 IU/kg cannot be reached.**
- **In subjects receiving standard or modified prophylaxis, the individual subject´s treatment and dosing regimen will be used for IR determination during the optional additional visits. The total dose and potency of the vials used for IR determination will be consistent with the vials used for routine (home) treatment (ie, any potency may be administered).**

11.1.1 Determination of Incremental Recovery Over Time in Subjects Transitioning from BAX326 Pivotal or BAX326 Pediatric Study

FIX levels to determine IR will be assessed at the following visits:

- At screening
- Every 3 months ± 1 week
- At study termination/completion

Subjects will be infused with 75 ± 5 IU/kg of BAX326. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. All assessments should be done at least 5 days after the previous dose of BAX326, and the subject must not actively bleed. The procedures for blood sampling are described in Section 11.1.6.

Table 11.1-1
Time Points of Determination of FIX Activity

Assessment of recovery	Pre-infusion	0-30 minutes prior to infusion
	Infusion of 75 ± 5 IU/kg BAX326	
	Post-infusion	30 minutes ± 5 minutes

The sample for measurement of FIX activity will be obtained from an extremity different from that used for the infusion of IP.

11.1.2 Determination of PK for PK-Tailored Dosing

An abbreviated PK will be performed in subjects who will receive a PK-tailored dosing and who have not undergone a PK study either in BAX326 Pivotal 250901 or BAX326 Surgery 251002. Blood samples for the PK evaluation will be collected at the time points shown in Table 11.1-2.

Table 11.1-2
Time Points for Measurement of FIX Activity for PK Assessment

Pre-infusion	0-30 minutes prior to infusion
Infusion of 75 ± 5 IU/kg BAX326	
Post-infusion	30 ± 5 minutes
	9 ± 3 hours
	24 ± 6 hours
	48 ± 6 hours
	72 (- 6) hours

Note: The PK assessment must be performed at least 5 days (120 hours), preferably 7 days, following the previous dose of a FIX product and the subject must not actively bleed.

Samples for measurement of FIX activity taken through 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP, using a 21- or 23-gauge thin-walled needle. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 2 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with 5 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

11.1.3 Determination of Incremental Recovery Over Time in Newly Recruited Subjects and Subjects Receiving a PK-Tailored Dose

FIX levels to determine IR will be assessed at the following visits:

- At ED1 (only newly recruited subjects)[xxi]
- At Week 4 ± 1
- At Month 3 ± 1 week
- Every three months ± 1 week
- At study termination/completion

Table 11.1-3
Time Points for Measurement of FIX Activity for IR Assessment

Pre-infusion	0-30 minutes prior to infusion
Infusion of BAX326, at dose of 75 ± 5 IU/kg or at the subject's individual PK-tailored dose, whichever is higher	
Post-infusion	30 minutes ± 5 minutes

Samples for measurement of FIX activity will be obtained from an extremity different from that used for the infusion of IP.

[xxi] For newly recruited subjects planned to receive a PK-tailored dose regimen ED1 corresponds to the PK visit.

11.1.4 Additional Determination of Incremental Recovery in Subjects Receiving Standard (Twice Weekly) Prophylaxis

In approximately 20 subjects, FIX activity will be also be determined at 4 additional time points during a 6-month period with regular, twice weekly prophylactic infusions, **without the requirement of a wash-out period.** In subjects aged < 12 years, additional IR determination is optional.

On 2 occasions, FIX activity should be assessed **3 days** after a prophylactic infusion of BAX326, ie, before and after the subsequent prophylactic infusion of BAX326, and on the other 2 occasions 4 days after a prophylactic infusion of BAX326, ie, during the subsequent prophylactic infusion of BAX326, as shown in Table 11.1-4.

Table 11.1-4
Time Points for Determination of Pre- and Post-Infusion FIX Levels During Regular, Twice-Weekly Prophylaxis

Example: **3 days** after last prophylactic infusion:		
Last prophylactic infusion approx 72 hours ago (eg: Monday morning)		
→ Subsequent prophylactic infusion approx 72 hours later (eg: Thursday morning):	Pre-infusion	0-30 minutes prior to infusion
	Infusion of regular prophylactic infusion	
	Post-infusion	30 ± 5 minutes
Example: **4 days** after last prophylactic infusion:		
Last prophylactic infusion approx 96 hours ago (eg: Thursday morning)		
→ Subsequent prophylactic infusion approx 96 hours later (eg: Monday morning):	Pre-infusion	0-30 minutes prior to infusion
	Infusion of regular prophylactic infusion	
	Post-infusion	30 ± 5 minutes

11.1.5 Additional Determination of Incremental Recovery in Subjects Receiving Modified or PK-Tailored Prophylaxis

In subjects receiving modified prophylaxis, FIX activity levels will also be determined within a 6-month period pre- and post-infusion at 4 different timepoints depending on the frequency of weekly prophylactic infusions **without the requirement of a wash-out period**. The pre- and post-infusion blood draws should occur such that they reflect the individual dosing interval. In subjects aged < 12 years, additional IR determination is not required.

Examples:

- Once weekly infusions: No additional IR determination is necessary, however, the regular study visit should be performed after a wash-out period of exactly 7 days to reflect the regular interval of 7 days.
- Twice weekly infusions: The schedule for blood sampling is described in Section 11.1.4.
- Three infusions per week, eg. Monday – Wednesday – Friday – Monday (2, 2 and 3 days)
  - On 2 occasions, FIX activity should be assessed 2 days after a prophylactic infusion of BAX326, ie, before and after the subsequent prophylactic infusion of BAX326, and
  - on the other 2 occasions 3 days after a prophylactic infusion of BAX326, ie, before and after the subsequent prophylactic infusion of BAX326 (see Table 11.1-4 for guidance).

11.1.6 Blood Sampling for Determination of Factor IX Level

At each blood sampling time point whole blood will be collected in S-Monovette® tubes (Sarstedt, Nümbrecht, Germany) containing 3.2% trisodium citrate, or equivalent blood drawing equipment (eg, Vacutainer tubes), and immediately mixed. **The citrated whole blood samples will be capped and transported at room temperature (ie, 20-25°C) to the local clinical laboratory for centrifugation, processing, and storage.** Monovettes must be kept in an upright position at all times to avoid leakage.

For all clotting assays, citrated whole blood will be spun in **a refrigerated centrifuge (2 to 8°C)** at ≥ 2000 x gravity for approximately 20 minutes in capped tubes **within 2 hours of collection**. The plasma supernatant will be re-centrifuged at the same rate and duration to ensure removal of platelets and other particulate matter.

At least three aliquots of 0.6 mL of the centrifuged, citrated plasma will be pipetted into appropriate storage tubes, capped, labeled, and **stored in a freezer at ≤ -70°C, ideally within 15 minutes, but no later than 30 minutes after processing.**

All citrated plasma samples will be stored and shipped to the central laboratory at ≤ -70°C for testing. All samples will be maintained capped to the greatest extent possible. All citrated plasma samples will be assayed for FIX activity using the one-stage aPTT-based assay method.

11.2 TGA Testing

Blood samples for TGA testing will be taken at the same time points as for FIX activity determination in a subset of subjects. Subjects will be infused with 75 ± 5 IU/kg of BAX326 during the regular study visits. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. The same criteria as described in Section 11.1 for determination of FIX activity also apply for TGA testing. TGA testing will only be performed in subjects 12 years and older.

11.2.1 Determination of TGA Parameters During PK

Blood samples for TGA parameters will be collected at the same time points as described in Section 11.1.1 for the PK assessment of FIX and are provided below in Table 11.2-1.

Table 11.2-1
Time Points for Determination of TGA Parameters During PK for FIX

Pre-infusion	0-30 minutes prior to infusion
Infusion of 75 ± 5 IU/kg BAX326	
Post-infusion	30 ± 5 minutes
	9 ± 3 hours
	24 ± 6 hours
	48 ± 6 hours
	72 (- 6) hours

Note: The assessment of TGA parameters must be performed at least 5 days (120 hours), preferably 7 days following the previous dose of a FIX product and the subject must not actively bleed.

Samples for measurement of TGA testing taken through 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP, using a 21- or 23-gauge thin-walled needle. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 2 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with 5 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

11.2.2 Pre- and Post-Infusion TGA Parameters Over Time in Subjects Receiving PK-Tailored Prophylaxis

TGA parameters will be determined pre- and post-infusion of BAX326 at the following visits in all or approximately 20 subjects ≥ 12 years and receiving PK-tailored prophylaxis:

- At ED 1 – for transitioning subjects who have undergone a PK study in BAX326 Pivotal, BAX326 Pediatric or BAX 326 Surgery
- At Week 4 ± 1
- At Month 3 ± 1 week
- At Month 6 ± 1 week

Table 11.2-2
Time Points for Determination of Pre- and Post-Infusion TGA Parameters Over Time

Pre-infusion	0-30 minutes prior to infusion
Infusion of BAX326, at dose of 75 ± 5 IU/kg	
Post-infusion	30 minutes ± 5 minutes

Samples for measurement of TGA parameters will be obtained from an extremity different from that used for the infusion of IP.

11.2.3 Additional Determination of TGA Parameters in Subjects Receiving Modified Prophylaxis

In addition, TGA parameters will also be determined within this 6-month period pre- and post-infusion at 4 different timepoints depending on the frequency of weekly prophylactic infusions **without the requirement of a wash-out period**. The pre- and post-infusion blood draws should occur such that they reflect the dosing interval. The TGA determination should coincide with the additional FIX activity level measurements as described in Section 11.1.5.

11.2.4 TGA Testing in Subjects Receiving Standard (Twice Weekly) Prophylaxis

In approximately 20 subjects, TGA parameters concurrent with the determination of pre- and post-infusion levels of FIX activity will be determined at 4 different time points during a 6-month period with regular, twice weekly prophylactic infusions, **without the requirement of a wash-out period**:

On 2 occasions, these should be assessed **3 days** after a prophylactic infusion of BAX326, ie, before and after the subsequent prophylactic infusion of BAX326, and on the other 2 occasions **4 days** after a prophylactic infusion of BAX326, ie, before and after the subsequent prophylactic infusion of BAX326, as shown in Table 11.2-3:

Table 11.2-3
Time Points for Determination of Pre- and Post-Infusion TGA Parameters During Regular, Twice-Weekly Prophylaxis

Example: **3 days** after last prophylactic infusion:		
Last prophylactic infusion approx 72 hours ago (eg: Monday morning)		
→ Subsequent prophylactic infusion approx 72 hours later (eg: Thursday morning):	Pre-infusion	0-30 minutes prior to infusion
	Infusion of regular prophylactic infusion	
	Post-infusion	30 ± 5 minutes
Example: **4 days** after last prophylactic infusion:		
Last prophylactic infusion approx 96 hours ago (eg: Thursday morning)		
→ Subsequent prophylactic infusion approx 96 hours later (eg: Monday morning):	Pre-infusion	0-30 minutes prior to infusion
	Infusion of regular prophylactic infusion	
	Post-infusion	30 ± 5 minutes

In addition, pre- and post-infusion TGA parameters will also be determined concurrent with FIX activity determination at the regular study visits during the 6- month period following a wash-out period and following administration of 75±5 IU/kg of BAX326 (ie, in total 3 times: at Month 3 ± 1 week, at Month 6 ± 1 week and at Month 9 ± 1 week).

11.2.5 Blood Sampling for TGA Testing

At each blood sampling time point, 3 mL of whole blood will be collected to obtain 2 aliquots of at least 0.6 mL. A detailed description of the blood sampling procedure and processing will be provided in the Laboratory Manual.

11.3 Hemostatic Efficacy

In all cases, the treatment with BAX326 will be at the discretion of the investigator and will consist of one of the following treatment options:

- standard prophylactic treatment with twice weekly administrations of 50 IU/kg (range 40-60 IU/kg which may be increased to 75 IU/kg [≥ 12 years of age] or 40-80 IU/kg [< 12 years of age]),
- modified prophylaxis,
- PK-tailored prophylactic treatment based on subject's individual PK, or
- on-demand treatment only (not applicable for newly recruited subjects).

The regimen for prophylactic and on-demand treatment should be based on the guidance as provided in Section 8.6.3 'Description of Treatment'. The following information will be recorded by the subject, the subject's legal representative (for home treatment) or by authorized, qualified personnel at the participating site (for hospital-based treatment in case of a bleeding episode):

- Location of bleed, ie, joint, soft tissue, muscle, body cavity, intracranial, other
- Type of bleed, ie, spontaneous, injury, unknown
- Severity of bleed, ie, minor, moderate, major, life/limb threatening
- Date and time of onset of bleed
- Date and time of each infusion of BAX326 required to achieve adequate hemostasis
- Date and time of resolution of bleeding episode

  Note:

  It is critical to inform the subject that 'resolution of bleed' means 'cessation of bleed' and not 'cessation of all bleed-related symptoms'.

- Type and number of analgesics required
- Overall clinical efficacy rating according to the rating scale as described in Table 11.3-1 at resolution of bleed.

Table 11.3-1
Rating Scale for Treatment of Bleeding Episodes

Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

If a bleed occurs following resolution of the bleed, it will be considered to be a 'new' bleed and recorded accordingly.

Subjects will resume their prophylactic treatment regimen the next scheduled day after the last therapeutic infusion for the treatment of a bleeding episode.

Details pertaining to all home treatments for each bleed, including response to treatment, will be recorded by study subjects or the subject's legal representative in subject diaries provided by the study sponsor. At each study visit the investigator will review together with the subject the response to treatment and evaluate the hemostatic efficacy rating. Any inconsistency between the efficacy rating and the number of infusions required to treat a bleeding episode, or a response to treatment rated as "none" must be immediately clarified. If two or more responses to treatment are rated with "fair", the investigator may re-evaluate the dosing regimen, and the time from bleeding onset to start of treatment. In case more than one infusion was given to treat a bleeding episode, but the treatment was rated with "excellent", information should be provided about the severity of the bleeding episode and/or whether additional infusions were given to maintain hemostasis. If infusions were given to maintain hemostasis after resolution of bleed, this should be recorded accordingly in the eCRF. **It is important to clearly indicate after which infusion the bleed stopped.** This may not necessarily coincide with the cessation of objective signs of bleeding, such as pain or swelling, since the absorption of blood would still be ongoing. Particularly in the case of severe hemophilic arthropathy and/or previous

joint surgery combined with severe bleeds, it is more difficult to define exactly the time point of the cessation of the bleed. If pain persists despite several infusions of BAX326, the presence of a bleed should be verified. It may become necessary to re-discuss the rating with the subject to ensure that the Rating Scale is fully understood. Cases of bleeding episodes requiring only one infusion but with a response to treatment rated with “fair” should also be evaluated.

If, at any time during the course of the study, a subject’s bleeding episode does not adequately respond to BAX326 therapy, he/she will be evaluated for the presence of inhibitory or total binding antibodies to FIX and clinically managed at the discretion of the investigator (see Section 12.7.1). In addition, AEs and the details of concomitant medication use coincident with the treatment of all acute bleeds will be recorded. Note that bleeding episodes are not to be reported as AEs (Section 12.3). Any non-study FIX therapy or hemostatic product use administered for a bleeding event will be recorded on the appropriate section of the subject’s diary and the eCRF. The use of a FIX concentrate other than BAX326 will disqualify the subject from further participation in the study.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

Events that do not necessarily meet the definition of AEs, regardless of causal association with IP, should be treated as AEs because they may be reportable to regulatory authorities according to AE reporting regulation; these include the following:

- IP overdose, whether accidental or intentional
- IP abuse
- An event occurring from IP withdrawal
- Any failure of expected pharmacological action
- Exposure to IP during pregnancy
- Unexpected therapeutic or clinical benefit from the IP

Any AE which has occurred in the BAX326 pivotal, surgery, or pediatric study and is still present at the time of enrolment to this study will be considered as an “ongoing AE” and will be recorded accordingly in the respective eCRF.

For the purposes of this study, the following events will **not** be considered an AE, and thus, not included in the analysis of AEs:

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be assessed as part of the efficacy assessments. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (eg, abrasion of skin). Therefore, any hemophilia-related event (eg, hemarthrosis [presenting as swelling, pain, and decreased range of motion], bruising, hemorrhages, or pain at bleeding episode site) will not be reported as AEs. However, the investigator may decide that the event is an AE if the event also would have occurred in a normal patient under the same circumstances.

- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

12.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
  - Anaphylaxis
  - Thrombo-embolic event
- Any inhibitor with a titer ≥ 0.6 BU confirmed by the central laboratory must be reported as an SAE. Only one initial SAE report per subject needs to be recorded in case an inhibitor is confirmed. Pertinent follow-up information (eg, new inhibitor results from the central laboratory) must be reported as a follow-up SAE.

Please note: Hospitalization due to elective surgery should **not** be reported as an SAE.

12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, IB, package insert). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

For the purposes of this study, all AEs, including unexpected AEs, experienced by a subject undergoing any study-related procedures will be recorded on the AE eCRF.

12.1.1.4 Preexisting Diseases

Preexisting diseases that are present before entry into the study, described in the medical history, and that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity or duration of a preexisting disease, the event must be described on the AE eCRF.

12.1.2 Assessment of Adverse Events

Each AE from the time of signed informed consent until study completion or date of discontinuation will be described on the AE eCRF (ie, 1 AE per form) using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure as defined in Section 12.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related/associated (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated to the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related/associated (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related/associated (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related/associated (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
    - Another etiology is unlikely or significantly less likely.

For each SAE assessed as ‘not related/associated‘ or ‘unlikely related/associated‘, the investigator shall provide an alternative etiology on the SAE report form.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences Not Considered Adverse Events

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAE Report. These events will not be considered as SAEs or included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from 2 weeks before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

Any AE which has occurred in the BAX326 pivotal, pediatric or surgery study and is still present at the time of enrolment to the current study will be considered as an "ongoing AE" and not as Medical History and will be recorded accordingly in the respective AE eCRF. Also, data on ongoing drug and non-drug therapy of these subjects will be used from the eCRF of these studies, updated, if applicable, and transcribed into the respective eCRF of the continuation study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 21.2), a physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. Height (in cm or inches) and weight (in kg or lb) will be measured at screening

At screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. In particular, the musculo-skeletal system including the target joints should be carefully described and documented. A target joint is defined as one in which there have been ≥ 4 bleeds in the 6 months prior to study entry or during the last 6-month period being in the study. Subjects will also be examined for the presence of target joints every 3 months±1 week. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Refer to the laboratory manual for information on collection and processing of samples. At the screening visit, wherever possible, the results from the completion/termination visit of Study 250901 (pivotal) or 251101 (pediatric) will be used to assess eligibility, and transcribed into the CRF, in place of drawing an additional sample.

12.7.1 Immunology Tests

The following immunology tests will be performed:

- Total binding and inhibitory antibodies to FIX[xxii]
- Antibodies to CHO proteins and rFurin[xxii]

The schedule for the immunology tests is shown in Table 12.7-1. All immunology tests should be performed after a wash-out period of at least 72 h after the last dose of BAX326 and subjects should not be actively bleeding.

[xxii] Indeterminate antibodies are considered negative and will therefore not be reported.

Table 12.7-1
Schedule of Immunology Tests

Subjects transitioning from BAX326 Pivotal (250901) or BAX326 Pediatric Study (251101)

- At screening (≈ results from the completion/termination visit of Study 250901 or 251101)
- Every 3 months ± 1 week
- At study termination/completion
- Whenever clinically indicated, eg, lack of response to treatment, or severe allergic reactions such as anaphylaxis

Newly recruited subjects:

- At screening
- At ED1/PK prior to the first infusion
- Week 4±1 week
- Month 3 ± 1 week
- Thereafter, every 3 months ± 1 week
- At study termination/completion
- Whenever clinically indicated, eg, lack of response to treatment, or severe allergic reactions such as anaphylaxis

12.7.1.1 Testing for Inhibitory and Total Binding Antibodies to Factor IX

Testing for inhibitory anti-FIX antibodies will be performed on citrate-anti-coagulated plasma, prepared as described in Section 11.1.6. All plasma samples will be tested using an assay based on the Nijmegen modification of the Bethesda method [36;37;38] in the central laboratory. Local laboratory results are to be used by the investigator for the clinical management of the subject, if applicable. When the results of the FIX inhibitor assay in the central laboratory and the local hemostasis laboratory are discordant, the result from the central laboratory will take precedence and be used in all analyses. Inhibitory anti-FIX antibodies will be further characterized as described in Section 12.7.1.2.

Testing for total binding anti-FIX antibodies will be performed on citrate-anti-coagulated plasma, prepared as described in Section 11.1.6, using an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human immunoglobulins (IgG, IgM, IgA, IgD) antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results. Samples that show a binding antibody titer ≥ 1:80 will be further analyzed as described in Section 12.7.1.2.

12.7.1.2 Development of Inhibitory or Total Binding Antibodies to FIX

If an inhibitory antibody with a titer ≥ 0.6 BU is detected, the inhibitor will be confirmed in the central laboratory within 2 weeks of study site notification of the original central laboratory result. Subjects who develop an inhibitor that changes from a low to a high titer inhibitor or from a high titer to a low titer upon a second evaluation should return to the study site for a third inhibitor test with a suggested minimum wash-out phase of 72 hours within 2 weeks of the second inhibitor assessment. Once a low (0.6 to 5 BU) or a high titer (> 5 BU) inhibitor is confirmed, the subject will be withdrawn from the study. Any inhibitor confirmed by the central laboratory must be recorded as an SAE (Section 12.1.1.1).

If total binding antibodies with a positive titer of 1:80 or more are detected, an additional blood sample will be drawn at the next study site visit, but within 2 ± 1 weeks to confirm the result. Subjects developing total binding antibodies with a titer ≥ 1:80 will continue in the study.

The following tests will be performed at the time of the confirmatory testing to investigate the nature of the inhibitory or total binding antibodies:

- IgG subtypes (IgG1, IgG2, IgG3, IgG4), IgM, and IgA using a semi-quantitative method
- High-sensitive C-reactive protein (hs-CRP) as a marker of the innate immune system using the Immulite® assay
- Additional markers may be considered, if applicable

To verify the FIX inhibitor, additional testing might be initiated, such as anti-phospholipid antibodies and lupus anticoagulans and/or FIX antibody testing using a different methodology, if necessary. Additional testing may be performed using remaining aliquots or back-up samples, for example for epitope mapping (see Section 12.7.6).

All tests will be performed at a defined central laboratory.

12.7.1.3 Antibodies to Chinese Hamster Ovary Proteins and rFurin

Citrated plasma will be assayed for the presence of antibodies to CHO protein and rFurin:

- **Antibodies to CHO Protein:** For this assay, CHO protein derived from cultures of untransfected cells will be used. Testing for binding anti-CHO protein antibodies will be done on citrate-anti-coagulated plasma (prepared as described in Section 11.1.6) using an ELISA employing polyclonal anti-human IgG antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.
- **Antibodies to rFurin:** An ELISA for detection of antibodies to human rFurin will be conducted. Testing for binding anti-human rFurin protein antibodies will be done on citrate-anti-coagulated plasma (prepared as described in Section 11.1.6) using an ELISA employing polyclonal anti-human IgG antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.7.2 Development of Severe Allergic Reactions and Anaphylaxis

In very rare cases, subjects with hemophilia B may develop severe allergic reactions following exposure to a FIX concentrate manifesting as pruritus, urticaria, erythema, angioedema, and/or dyspnea, which may progress to a life-threatening anaphylaxis with bronchospasm and hypotension. These reactions may occur concurrently or prior to the development of a FIX inhibitor (see Section 6.2).

Blood samples will be drawn for the following tests to be performed at the central laboratory:

Within 1 hour, if feasible, and 24 h following the severe allergic reaction/ anaphylaxis:

- hs-CRP
- Immune complexes: Two assays will be used to determine the presence of circulating immune complexes (CIC):
  - CIC-C1q: The MicroVue CIC-C1q assay uses highly pure, functional human C1q coated in the solid phase to capture immune complexes. In the first stage, CIC in the diluted patient samples and heat-aggregated gamma globulin in the controls and standards are dispensed into the C1q coated assay wells. After incubation, unbound material is removed in a washing step and a ready-to-use conjugate (goat anti-human Ig-HRP) is added. After a second incubation, unbound conjugate is washed away

After addition of a substrate and a short incubation interval, the quantity of CIC in the sample (µg Eq/ml) can be determined by comparison to a standard curve.

- CIC-C3: The MicroVue CIC-Raji Cell Replacement ELISA assay uses a proprietary monoclonal antibody to a common neoantigen expressed on C3d, iC3b, and C3d,g to capture C3d containing immune complexes in human serum or plasma. In the first stage, CIC in the diluted patient samples and HAGG in the controls and standards are dispensed into the coated assay wells. After incubation, unbound material is removed in a washing step and a ready-to-use conjugate is added. After a 30-minute incubation unbound conjugate is washed away. After addition of a substrate and a short incubation interval, the quantity of CIC in the sample (µg Eq/mL) can be determined by comparison to a standard curve.

- IgE: The presence of IgE will be determined by using the ImmunoCAP, a FIX-specific IgE blood test (Phadia®). The basis of the ImmunoCAP® technology is a cellulose polymer in a plastic capsule providing a large surface for protein binding. rFIX is covalently coupled to the solid phase using cyan-bromide activation of the cellulose polymer. Testing for binding IgE anti-human FIX antibodies will be done with 0.5 mL serum. Antibody-containing samples will be identified and titrated in a screening assay followed by a confirmatory assay to exclude false positive results.

After a minimum wash-out period of 72 hours following exposure to BAX326:

- Inhibitory and total binding anti-FIX antibodies.
- IgG subtypes (IgG1, IgG2, IgG3, IgG4), IGM, and IgA using a semi-quantitative method, if inhibitory or total binding anti-FIX antibodies are detected.
- Other assays may be considered.

Back-up blood samples drawn prior to the most recent infusion of BAX326 (see Section 12.7.6) will also be tested for the assays mentioned above to serve as baseline.

12.7.3 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), and leukocytes (ie, white blood cell count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet count.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

Blood will be obtained for assessment of hematology and clinical chemistry parameters at the following timepoints:

Subjects transitioning from BAX326 Pivotal or BAX326 Pediatric Study:

- Screening
- Every 3 months ± 1 week At study termination/completion
- Whenever clinically indicated, ie, in case of an AE

Newly recruited subjects:

- At screening
- Week 4 ± 1 week
- Month 3 ± 1 week
- Thereafter, every 3 months ± 1 week
- At study termination/completion
- Whenever clinically indicated, ie, in case of an AE

Hematology and clinical chemistry assessments will be performed on EDTA-anti-coagulated whole blood and serum, respectively, at the central laboratory. In addition, assessments may be performed whenever clinically indicated.

12.7.4 Urinalysis

A urine sample will be obtained for assessment of protein content using a dipstick at:

Subjects transitioning from BAX326 Pivotal or BAX326 Pediatric Study:

- Screening
- Every 3 months ± 1 week
- At study termination/completion
- Whenever clinically indicated, ie, in case of an AE

Newly recruited subjects:

- At screening
- Week 4 ± 1 week
- Month 3 ± 1 week
- Thereafter, every 3 months ± 1 week
- At study termination/completion
- Whenever clinically indicated, ie, in case of an AE

A urinalysis should also be performed if inhibitors are detected or whenever clinically indicated. Urinalysis will be performed at the central laboratory.

12.7.5 Other Laboratory Tests

12.7.5.1 Other Laboratory Tests at Screening

The following blood samples will be obtained at the specified time points; all tests will be performed at the central laboratory. These tests also need to be performed in newly recruited subjects.

- FIX activity level (newly recruited subjects) to determine eligibility
- FIX antigen level
- FIX antigen will be measured using a commercially available ELISA kit. The samples will be prepared as described in Section 11.1.6.
- Assessment of gene mutations and human leukocyte antigen (HLA) genotype:
  To test for FIX gene mutations, the cell pellets (buffy coat and erythrocytes) from the initial FIX activity sample will be retained after collection of the plasma supernatant (Section 11.1.6). Cell pellets will be labeled and stored at ≤ -70°C. FIX gene mutation and HLA genotype testing will be performed at the central laboratory.

The results will be provided to the sites. The investigator will be responsible for informing the subject of the test results. If results of FIX gene mutation analysis and HLA genotype are already available at the study site, they will be provided to the sponsor and an additional analysis will not be required.

- Prothrombotic markers (TAT complexes, D-dimers, Prothrombin fragment 1.2):
  Plasma samples will be collected as described in Section 11.1.6 (blood sampling for the determination of FIX level, but frozen at -20°C). The tests will be performed at the central laboratory.
  Prothrombotic markers should also be determined whenever clinically indicated.
- CD4 count:
  At screening, and every 12 months, a CD4+ lymphocyte count will be performed on EDTA-anti-coagulated whole blood at the central laboratory to confirm the subject's continued eligibility.
- Viral load, if HIV positive:
  In HIV positive subjects, a measurement of the viral load will be performed.
- Pregnancy Test:
  A pregnancy test for females of child-bearing potential will be performed. The pregnancy test may need to be repeated during the course of the study in countries where mandated by national law.

12.7.6 Assessment of Laboratory Values

12.7.6.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value is to be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value consitutes a new AE (see definition in Section 12.1). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE eCRF. If the value is not deemed an AE, the investigator will indicate on the eCRF the reason, ie, because it is due to a lab error, is due to a preexisting disease (described in Section 12.1.1.4), is a symptom of a new/worsened condition already recorded as an AE, or is due to another issue that will be specified.

Note: For abnormal values not considered clinically significant, no further action is necessary. However, additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Laboratory values for FIX activity and FIX antigen will not be assessed by the investigator for clinical significance as it is understood that these are abnormal for this patient population.

12.7.7 Biobanking

At all visits, an additional blood sample should be drawn prior to the infusion of BAX326 as a back-up sample for additional testing, as clinically indicated, and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, tests required per regulatory guidelines, further evaluation of an AE, or follow-up of other test results. The same sampling and processing procedures should be followed as described in Section 11.1.6 for citrated plasma. An additional blood sample will also be drawn and processed for serum. For subjects < 6 years of age, back-up samples are optional; for subjects < 12 years of age, back-up samples for serum are optional.

Blood samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test or an AE). Samples will be stored in a coded form until completion of the final clinical study report (CSR) and will be destroyed within 12 months after completion of the CSR.

12.8 Vital Signs

Vital signs will include body temperature (ºC or °F), respiratory rate (breaths/min), pulse rate (beats/min), and supine systolic and diastolic blood pressure (mmHg).

Vital signs will be measured at the following timepoints:

Subjects transitioning from BAX326 Pivotal or BAX326 Pediatric Study:

- Screening
- Every 3 months ± 1 week
- At study termination/completion
- Whenever clinically indicated, ie, in case of an AE

Newly recruited subjects:

- At screening
- At ED1
- Week 4±1 week
- Month 3 ± 1 week
- Thereafter, every 3 months ± 1 week

- At study termination/completion
- Whenever clinically indicated, ie, in case of an AE

Subjects receiving PK-tailored dosing:

- During PK: within 15 minutes of start of infusion of 75±5 IU/kg BAX326 and at 30±5 minutes and 2 h ± 10 minutes following the infusion

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. If the abnormal value was not deemed an AE, the investigator will indicate the reason on the source record, ie, because it was due to an error, due to a preexisting disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Data Monitoring Committee

The safety of BAX326 in this study will be monitored by an independent Data Monitoring Committee (DMC) as scheduled until the end of 2015. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of hemophilia clinical care and research who are not actively recruiting subjects, and an independent statistician.

The sponsor will formally convene this panel for review of the study data at least once per year until completion of the study. From the beginning of 2016onwards, the DMC chair will no longer review all SAEs for all subjects as sufficient positive safety data from pre- and post-marketing BAX326 exposures are already available.

The study may be stopped at any time by the sponsor in case of unacceptable risks to subjects, in particular in case of inhibitor development, thrombotic events, or anaphylaxis.

13. ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE

13.1 Rationale for Selection of Health-related Quality of Life Instruments

Currently, there is little published literature on the HR QoL in patients with hemophilia B. The BAX326 continuation study will enable a a prolonged observation period in those subjects who completed BAX326 Pivotal or BAX326 Pediatric. By capturing generic HR QoL, the impact of prophylaxis and treatment will be assessed on the patient's overall health, such as their ability to perform various activities, the impact on their emotional functioning, and their overall mental health. Capturing these data using a standardized, generic instrument will allow comparisons to be made with populations suffering from other chronic conditions.

By also assessing hemophilia-specific HR QoL, the impact of prophylaxis and treatment will be assessed on how patients feel about their ability to control their bleeds, pain from swellings, joint pain, and worries about their ability to live normally with their condition. The Haemo-QOL/Haem-A-QOL instruments have been developed and used in hemophilia A patients; capturing these data will allow comparisons to be made with hemophilia A populations.

Other measures, such as health resource use and the EQ-5D, will enable health utility and resource utilization data to be captured for input into future cost-effectiveness analyses.

Finally, subjects will be asked to estimate their patient activity level. Patient activity level will be captured using the Leisure Time Exercise Questionnaire which captures intensity and frequency of exercise over the course of one week. These data will be collected for all age groups. This data will be useful to understand how active hemophilia B patients are and may help to explain differences in bleeding rates for patients receiving BAX326 prophylaxis.

The Health Resource Utilization consists of a set of 4 questions as described in Table 13.2-1.

13.2 Assessment of Health-related Quality of Life and Health Resource Use

The assessment of HR QoL based on 4 questionnaires will be performed **every 6 months ± 1 week.** Newly recruited subjects will have their first HrQoL assessment including Patient Activity Level performed prior to or following the first infusion with BAX326, thereafter every 6 months.

The capture of health resource use will be performed by a named member of study site staff **every 3 months ± 1 week**. Newly recruited subjects will have their first health resource use capture prior to or following the first infusion with BAX326, thereafter at every 3 months ± 1 week.

Note that due to the unavailability of linguistically validated translations of certain HRQoL measures in certain countries, some of these questionnaires may not be administered in all countries participating in this study.

For subjects who are 2 to 7 years of age on the day of enrolment into Pediatric Study 251101, the PedsQL (Parent-proxy versions for ages 2-4 and 5-7), patient activity level, and health resource utilization will be measured. For subjects between 8 and 11 years of age on the day of enrolment into Study 251101, the Haemo-QOL (short version), PedsQL (child version), patient activity level, and health resource utilization will be measured.

For subjects aged 12 to 16 years on the day of enrolment into Pivotal Study 250901 (ie, the date the informed consent signed), the Haemo-QOL, PedsQL, EQ-5D, VAS Pain Scale, patient activity level, and health resource utilization will be measured. For subjects aged 17 and older, the Haem-A-QOL (adult version), SF-36, EQ-5D, VAS Pain Scale, patient activity level, and health resource utilization will be measured. These questionnaires are described in the sections below.

Cohort 1 subjects will continue using the same HRQoL questionnaires used in the parent study, even if they transition to an older age group in this study.

Cohort 2 subjects will continue using the same HRQoL questionnaires used at their Screening Visit for Study 251001 even if they transition to an older age group later in this study.

Table 13.2-1 depicts the specific domains within each instrument where potential differences over time due to the treatment may be expected. These should be considered as exploratory since it remains uncertain whether differences will be demonstrated and the study is not powered for these endpoints. Given that most subjects are moving from on-demand treatment to prophylaxis, and some patients will have longer than 6 months on prophylaxis, it is conceivable that differences might be seen.

Table 13.2-1
Potential Outcomes from HR QoL Measures

Instrument	Description	Potential Change/Impact
SF-36 (patients 17 and older) 36 items	The SF-36 is a validated, generic HR QoL instrument, measuring physical, emotional, social functioning as well as overall general health. It captures the following 8 domains: Role Physical (RP) Bodily Pain (BP) Physical Functioning (PF) General Health (GH) Vitality (VT) Social Functioning (SF) Role Emotional (RE) Mental Health (MH)	In this trial, differences may be demonstrated in the following domains: 1. Role Physical – This captures limitations in the kind of work or usual activities and reductions in amount of time spent on, or difficulty performing, work or other usual activities. With patients now receiving prophylaxis, they may be more willing to do activities that they may have avoided before in fear of a bleed. 2. Social functioning - This 2-item scale assesses the impact of physical and/or emotional problems on the quantity and quality of social activities. After 6 months on prophylaxis, patients may participate more in activities, such as sports that they might have avoided in the past, and thus, report improved social functioning as a result. 3. Bodily Pain - This assesses the intensity of bodily pain and the extent that pain interferes with normal work activities. It is not clear whether general pain will be reduced in 6 months, however, it may be shown that pain has not worsened over the 6 months on prophylaxis.
Peds-QL Parent-Proxy Ages (years) 2-4, 5-7, and Child report 8-12 and 12-16 years old 23 items	The Peds-QL is a generic HR QoL instrument designed specifically for a pediatric population. It captures the following domains: Physical Functioning Emotional Functioning School Functioning Social Functioning Psychosocial Summary Physical Health Total Score	In this trial, differences in the following areas may be demonstrated: 1. Physical activities –Ability to do sports or other exercise, overall aches/pain, low energy 2. Emotional functioning – Worry about future/what will happen to self 3. Social functioning – Being able to participate in things other kids are doing 4. School functioning – Missing school due to doctor/hospital visit

Table 13.2-1
Potential Outcomes from HR QoL Measures

Instrument	Description	Potential Change/Impact
Haemo-QoL (8-16 year olds)/Haem-A-Qol (17 and older) Haemo-QOL – 35 items Haem-A-QOL - 46 items	This instrument is a hemophilia-specific instrument that captures the following HR QoL domains: • Physical health • Feelings/emotional • View of self • Sports/leisure • School/work • Dealing with hemophilia • Treatment • Future • Family planning • Relationships	As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. Differences after 6 months of prophylaxis may be expected in many areas: 1. Physical health – Captures pain in joints, swelling pain, difficulty walking and needing extra time to prepare for activities. 2. Sports/leisure – Refrain from sports, restricted travel, needing to plan everything in advance 3. School/work – Everyday activities impeded due to hemophilia 4. Dealing with hemophilia –Ability to control bleeds 5. Future – Afraid of needing a wheelchair, worry about worsening condition, difficulty in leading a normal life
EQ-5D 6 items	This instrument captures overall HR QoL; a health utility score can be calculated from this measure. There are adult and proxy versions. It captures physical, mental, and social functioning.	The primary reason to administer this instrument is to obtain health utility data, which may serve for input into a cost-effectiveness analysis, in case a cost-effectiveness model is developed.
VAS General Pain Assessment 1 item	This is a VAS that assesses general pain over the past 4 weeks.	While a reduction in acute pain due to a bleed may be expected, it is uncertain whether 6 months of prophylaxis treatment will be able to reduce general, chronic pain in this patient population.
Leisure Time Exercise Questionnaire	This question captures intensity and frequency of exercise over one week.	This will allow an understanding of paitent activity levels in our trial population and test for an association between ABR and patient activity level.

Table 13.2-1
Potential Outcomes from HR QoL Measures

Instrument	Description	Potential Change/Impact
Health resource use items 4 items	Thi--s information will be gathered by the sites as part of the eCRF, subjects will not have to complete a questionnaire. It assesses: • Number of days missed from work/school • Number and days of hospitalizations • Number of emergency visits to a hospital • Number of unscheduled visits to a general practitioner	This information is necessary to collect as input into a cost-effectiveness analysis that may be developed in the future.

14. STATISTICS

14.1 Sample Size and Power Calculations

The sample size is not based on statistical consideration and is determined by the number of subjects of the BAX326 pivotal protocol 250901 and the pediatric protocol 251101, who are willing to participate in this study and meet the eligibility criteria as well as regulatory requirements.

14.2 Datasets and Analysis Cohorts

The Full Analysis Set (FAS) will be comprised of all subjects who are exposed to any amount of IP. For subjects who discontinue before reaching 100 EDs, data will be included up through the day of discontinuation. The FAS will be used for all analyses.

14.3 Methods of Analysis

Missing data will be reported as missing. No techniques will be employed to adjust for missing data.

The pediatric (< 12 years) and the adolescent/adult (≥ 12 years) data will be summarized separately, if appropriate. Further analyses will occur between the age cohorts < 6 years and 6 to < 12 years, if applicable.

Safety and efficacy data from the additional BAX326 naïve subjects (Cohort 2) will be analyzed together with the data from the previously treated subjects (Cohort 1).

14.3.1 Primary Outcome Measure

The analysis of AEs possibly or probably related to IP that occurred during or after treatment application will be descriptive.

14.3.2 Secondary Outcome Measures

14.3.2.1 Hemostatic Efficacy

The efficacy of the IP in the treatment of bleeds will be summarized. It includes the overall hemostatic efficacy rating at resolution of bleed, and the number of infusions and the total weight-adjusted dose per bleeding episode.

The annualized rate of bleeding episodes (ABR) will be calculated by treatment regimen only for subjects who have adequate treatment time for bleeding rate assessment as follows: (Number of bleeding episodes / Observed treatment period in days)*365.25.

The observation period for prophylactic treatment will be the time between the first and the last prophylactic infusions.

Product consumption of the IP will be summarized during the study, including the average number of infusion and the average weight-adjusted consumption per months and per year, and the average weight-adjusted consumption per event (prophylactic infusion and bleeding treatment).

14.3.2.2 Pharmacokinetics

PK parameters will be calculated for all subjects planned to receive a PK-tailored treatment regimen using a non-linear mixed effects model approach.

The available PK data (FIX activity levels) from pivotal study 250901, pediatric study 251101 and surgery study 251002 will be utilized together in the model and strengthen the estimation of the full PK curve even if only sparse samples are available for an individual.

The following PK parameters for FIX will be reported using descriptive statistics: AUC0-∞ (area under the plasma concentration/time curve from time 0 to infinity),IR, T1/2 (elimination phase half-life), MRT (mean residence time), CL (clearance), Vss (Volume of distribution at steady state).Incremental recovery (IR) will be determined as the changes in FIX activity level from pre-infusion to 30 ± 5 minute post-infusion, divided by dose, and reported as (IU/dL)/(IU/kg). FIX activity levels at pre-infusion reported as < 1% will be used as 0.5% for the calculation of IR.

Incremental recovery of FIX will be summarized by visit and displayed graphically over time for each subject. Also the change from baseline (at screening visit) will be described using summary statistics. As the maximum dose can be 120 IU/kg any doses higher than 120 IU/kg are not allowed and therefore frequencies requiring a higher are excluded.

14.3.2.3 Safety

Frequency counts and percentages will be calculated for the following variables: occurrence of inhibitory antibodies to FIX, occurrence of total binding antibodies to FIX, occurrence of antibodies to CHO proteins and rFurin, occurrence of severe allergic reactions (e.g. anaphylaxis), and occurrence of thrombotic events.

Analysis of AEs that occurred during or after treatment application will be descriptive. Serious and non-serious AEs will be cross-tabulated for severity and relation to the treatment, giving the number of AEs and the number (proportion) of unique subjects who experienced adverse events. All AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term.

Clinically significant changes in laboratory parameters and vital signs will be reported.

14.3.2.4 Health-related Quality of Life and Pharmacoeconomics

HR QoL assessments (SF-36/PedsQL, Haem-A-QoL/Heaemo-QoL, EQ-5D, and General pain assessment (VAS)), and the change from the baseline (at screening visit) will be summarized by visit. Analysis of patient activity level and health resource use will be descriptive in nature.

14.3.3 Exploratory Outcome Measures

TGA parameters (lag time, time to peak thrombin generation, peak thrombin generation, and ETP) will be summarized using descriptive statistics and displayed graphically.

The association of pre-infusion TGA parameters with pre-infusion FIX activity level and spontaneous bleeds during prophylaxis will be explored.

14.4 Safety Review

An interim safety review may be performed after a minimum of 50 subjects have accumulated a total of at least 100 EDs to BAX326 for evaluation of long-term hemostatic efficacy, safety, immunogenicity and HrQoL.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol, and in study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

16.1.1 Investigator Report and Final Clinical Study Report

The investigator will submit a written report of the study's status to the sponsor, as described in the Clinical Study Agreement. The investigator will also submit interim progress reports to the sponsor on a regular basis, as requested.

The coordinating investigator will sign the clinical study report. The coordinating investigator will be the one who enrolls most of the subjects in the study, and will be designated once the last subject has completed the study.

16.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

16.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

16.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

16.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject or when the change(s) involves only logistical or administrative aspects of the study (eg, change of study monitor, change of phone number). In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 5 working days after the change is implemented. The investigator will also notify the EC of the emergency change.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

16.6 Laboratory and Reader Standardization

Not applicable, a central laboratory/reader will be used for all laboratory assessments.

17. ETHICS

17.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

17.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The Investigator's Brochure will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

17.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 17.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. A separate consent form will be provided concerning genetic testing; if a subject does not wish to undergo genetic testing s/he may still participate in the remaining study procedures and assessments. Patients or their legally authorized representative(s) will be allowed

sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see paragraph above).

18. DATA HANDLING AND RECORD KEEPING

18.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

18.2 Study Documents and Case Report Forms

The investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include information defined as „source data“ (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, eCRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

18.2.1 Case Report Forms

The investigator is responsible for the procurement of data and for the quality of data recorded on the eCRFs. CRFs will be provided in electronic form.

Only authorized study site personnel will record or change data on the eCRFs. Changes to an eCRF will require documentation of the reason for each change. If data is not entered on the eCRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. An identical (electronic) version of the complete set of eCRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 18.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

18.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

19. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

20. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

21. SUPPLEMENTS

21.1 Flow Diagram of Study Procedures

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

1. Screening Visit

1a. Subjects Transitioning from the Pivotal 250901 or Pediatric 251101 Protocol

At the time of screening, at least 5 days (120 hours), preferably 7 days, must have elapsed since the previous FIX administration and the subject must not be actively bleeding.

The screening visit will be performed on the same day as the completion/termination visit of the 250901/251101 protocol, and the new informed consent will be obtained. To give the patient sufficient time to review the ICF, this document may be provided prior to the screening visit.

The relevant data obtained for the 250901/251101 completion/termination visit will be transcribed to the screening visit eCRF, and where possible, duplication of blood draws or evaluations will be avoided. Evaluations must be completed within 4 weeks ± 1 week of the screening visit. The following procedures will be carried out:

1) Informed consent
2) Assessment of eligibility
3) Hand out subject diary at enrolment
4) Presence of target joints
5) Dispense IP supply for a maximum of 4 weeks ±1 week

The following data, including ongoing AEs, will be obtained/transcribed from the 250901/251101 completion/termination visit:

6) Medical history, concomitant medication and non-drug therapy use
7) Physical examination including height and weight
8) Vital signs within 15 minutes of start of infusion
9) Laboratory results for:
    a) Immunology (pre-infusion of IP)
    b) Hematology and clinical chemistry
    c) CD4 count
    d) Viral load if the subject is HIV positive
    e) Urinalysis
    f) Pregnancy test (if applicable, and as appropriate)
10) Recovery assessment
    a) Pre-infusion blood draw for FIX activity within 0.5 h of start of infusion
    b) Infusion of 75 ± 5 IU/kg BAX326
    c) Post-infusion blood draw for FIX activity at 30 ± 5 minutes for subjects transitioning from BAX326 Pivotal

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

d) Post-infusion blood draw for FIX activity at 15-30 minutes for subjects transitioning from BAX326 Pediatric

11) Vital signs at 30 ± 5 minutes and 2 h ± 10 minutes following completion of the infusion

1b. Newly Recruited Subjects

At the time of screening, at least 5 days (120 hours), preferably 7 days, must have elapsed since the previous FIX administration and the subject must not be actively bleeding. Evaluations must be completed within 42 days of the screening visit. The following procedures will be carried out:

12) Informed consent
13) Hand out subject diary at enrolment and provide clear instructions how to fill out diary
14) Presence of target joints
15) Medical history and prior/concomitant medication history
16) Physical examination including height and weight
17) Vital signs
18) Blood draws for:
    a) FIX activity
    b) FIX antigen
    c) Immunology
    d) Hematology and clinical chemistry
    e) Gene mutation and human leukocyte antigen (HLA) genotype; if results already available at the study site, they will be provided to the sponsor, additional analysis not necessary
    f) CD4 count
    g) HIV test (antibodies against HIV types 1 and 2) and viral load, if positive
    h) Hepatitis serology (hepatitis A [anti-HAV IgG and IgM], hepatitis B [anti-HBs, antiHBc, HBsAg]), hepatitis C [anti-HCV])
    i) INR
    j) Pregnancy test (as appropriate, and to be repeated during the course of study in countries where mandated by national law)
    k) Prothrombotic markers (TAT complexes, D-dimers, Prothrombin fragment 1.2), to be repeated whenever clinically indicated during course of study
19) Urine sample
20) Assessment of eligibility

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

2. Assessment of PK in Subjects Receiving PK-Tailored Prophylaxis

Newly recruited subjects, once eligibility is confirmed, and subjects participating in the continuation study who did not have a PK performed in the BAX326 pivotal or surgery study will undergo an abbreviated PK to receive a PK-tailored dose regimen.

At least 5 days (120 hours), preferably 7 days, must have elapsed since the previous FIX administration and the subject must not be actively bleeding.

Procedures to be done **before the infusion**:

1) Review and discuss subject diary, re-training as needed
2) Record AEs
3) Concomitant medication and non-drug therapy
4) Physical examination
5) Pre-infusion blood draw within 0.5 h of start of infusion: FIX activity, TGA parameters, if applicable
   - Immunology (newly recruited subjects only)
6) Vital signs within 15 minutes of start of infusion
7) Assess HR QoL including Patient Activity Level and collect Health Resource Utilization items pre- or during the 66-72 h period following the infusion of BAX326 in newly recruited subjects

Infusion and post-infusion procedures:

1) Infusion of 75 ± 5 IU/kg BAX326 at an infusion rate not to exceed 10 mL/min.
2) Blood draws for FIX activity and TGA parameters, if applicable, at 30 ± 5 minutes, 9 ± 3 h, 24 ± 6 h, 48 ± 6 h and 72 (- 6) h following the infusion
3) Vital signs at 0.5 h ± 5 minutes and 2 h ± 10 minutes following completion of the infusion (before blood sampling at these time points)
4) Dispense IP supply for up to 4 weeks until the weekly dose, based on the subject's individual PK and calculated by the sponsor, is available at the study site. In the interim, the dose regimen will be at the discretion of the investigator.

Throughout: AEs and concomitant medication and non-drug therapy use.

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

3. First Infusion in Newly Recruited Subjects (ED1)

Once eligibility criteria are confirmed, the subject will receive the first infusion at the study site which will include an assessment of IR. For subjects planned to receive a PK-tailored dose regimen, please see procedures described for assessment of PK.

At least 5 days (120 hours), preferably 7 days, must have elapsed since the previous FIX administration and the subject must not be actively bleeding.

Procedures to be done **before the infusion**:

1) Review and discuss subject diary
2) Record AEs
3) Concomitant medication and non-drug therapy
4) Physical examination including weight
5) Assess HR QoL including Patient Activity Level and collect Health Resource Utilization items pre- or post-infusion of BAX326
6) Vital signs within 15 minutes of start of infusion

Determination of FIX Recovery (and TGA parameters, if applicable)

1) Pre-infusion blood draw for FIX activity (and TGA parameters, if applicable) within 0.5 h of start of infusion
   - Immunology
2) Infusion of BAX326, at dose of 75 ± 5 IU/kg at a rate not to exceed 10 mL/min
3) Post-infusion blood draw for FIX activity (and TGA parameters, if applicable) at 30 ± 5 minutes
4) Vital signs at 30 ± 5 minutes and 2 h ± 10 minutes following completion of the infusion
5) Dispense IP supply for a maximum of 4±1 week
6) Hand-out of subject diary

Throughout: AEs and concomitant medication and non-drug therapy use.

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

4a. Study Visit Week 4±1 in Newly Recruited Subjects

The Week 4 ± 1 visit must be arranged so that there is a wash-out period of at least 5 days (120 hours), preferably 7 days, from the previous dose of BAX326. The subject must not be actively bleeding.

The following procedures will be carried out:

Prior to recovery assessment:

- Review and discuss subject diary, re-training as needed
- Revuew and discuss the number of spontaneous bleeding episodes
- Record AEs
- Concomitant medication and non-drug therapy use
- Collection of Health Resource Utilization items
- Physical examination
- Blood draws for:
  - Immunology (pre-infusion of IP)
  - Hematology and clinical chemistry
- Urine sample for urinalysis
- Vital signs within 15 minutes of start of infusion

Determination of FIX recovery (and TGA parameters, if applicable)

a) Pre-infusion blood draw for FIX activity (and TGA parameters, if applicable) within 0.5 h of start of infusion
b) Infusion of BAX326, at dose of 75 ± 5 IU/kg at a rate not to exceed 10 mL/min
c) Post-infusion blood draw for FIX activity (and TGA parameters, if applicable) at 30 ± 5 minutes
d) Vital signs at 30 ± 5 minutes and 2 h ± 10 minutes following completion of the infusion

- Hand out subject diary
- Dispense IP supplies for a maximum of 2 months

Throughout: AEs and concomitant medication and non-drug therapy use.

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

4b. Study Visit Week 4 ± 1 in Subjects Transitioning from BAX326 Pivotal or BAX326 Pediatric Study

This visit should occur upon availability of the laboratory results within 4 ±1 weeks following screening. For subjects switching back to this study from the surgery study[xxiii], the respective visit window may be extended from ± 1 week to ± 2 weeks.

At this study visit the following procedures will be carried out:

1) Review and discuss subject diary
2) Record AEs
3) Concomitant medication and non-drug therapy use
4) Hand out subject diary
5) Dispense IP supplies for 2 months

Throughout: AEs and concomitant medication and non-drug therapy use.

5. PK-Tailored Dosing:

5a. Start of PK tailored treatment regimen

Subjects will be contacted by the investigator regarding the dose and treatment regimen of the PK tailored regimen upon availability of PK results. Subjects to start PK tailored treatment regimen 4±1 weeks prior to the next 3 monthly visit

5b. Phone Calls by Study Site to Subjects

Phone calls from study sites to subjects have to occur at:

- 8 weeks ± 1 week
- 17 weeks ± 1 week and
- 22 weeks ± 1 week following the first PK-tailored dose at study site.

The following information is to be requested by the site and entered into eCRF:

- Occurrence of bleeding episodes, exact location and cause
- Occurrence of AEs

[xxiii] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

APPLICABLE TO ALL PROPHYLACTIC REGIMENS THROUGHOUT THE STUDY:

Dose and/or frequency adjustments should be performed if a subject meets either of the following criteria:

- **Two or more spontaneous** (not related to trauma) bleeding episodes in the same target joint within any 3-month period, **OR**
- **One or more spontaneous** (not related to trauma) bleeding episodes in a non-target joint or a non-joint within any 3-month period

In such a case, the dose and/or frequency will be increased. It is recommended to consult the sponsor.

In subjects with severe hemophilic arthropathy and/or target joints who continue experiencing recurrent bleeding episodes despite adjustments of the prophylactic dose and/or dosing frequency, an ultrasound of the affected joint(s) should be performed to verify the presence of a bleed.

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

6. Study Visits Every 3 Months ± 1 Week Following Screening in Subjects Transitioning from BAX326 Pivotal or BAX326 Pediatric Study; Study Visits Every 3 Months ± 1 Week Following ED1 for Newly Recruited Subjects

Each visit must be arranged so that there is a wash-out period of at least 5 days (120 hours), preferably 7 days, from the latest dose of BAX326. The subject must not be actively bleeding. For subjects switching back to this study from the surgery study[xxiv], the respective visit window may be extended from ± 1 week to ± 2 weeks.

At each study visit the following procedures will be carried out:

Prior to the recovery assessment:

- Review and discuss subject diary
- Review and discuss the number of spontaneous bleeding episodes
- Review number of EDs to BAX326
- Record AEs
- Concomitant medication and non-drug therapy use
- HR QoLincluding Patient Activity Level pre- or post-infusion of BAX326 – every second visit (every 6 months ±1 week)
- Collection of Health Resource Utilization items
- Physical examination
- Occurrence of target joints
- Blood draws for:
  a) Immunology (pre-infusion of IP)
  b) Hematology and clinical chemistry
- Urine sample for urinalysis
- Vital signs within 15 minutes of start of infusion
- CD4 count will be assessed **once a year.**
- **Assessment of FIX Recovery (and TGA parameters, if applicable)**
  a) Pre-infusion blood draw for FIX activity (and TGA parameters, if applicable) within 0.5 h of start of infusion
  b) Infusion of 75 ± 5 IU/kg BAX326 at a rate not to exceed 10 mL/min
  c) Post-infusion blood draw for FIX activity (and TGA parameters, if applicable) at 30 ± 5 minutes
  d) Vital signs at 30± 5 minutes and 2 h ± 10 minutes following completion of the infusion

[xxiv] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

In all subjects receiving modified or PK-tailored prophylactic treatment (or approximately 20 subjects) and in a subset of approximately 20 subjects on twice-weekly standard with BAX326, TGA testing concurrent with IR determination will be performed at 3 regular 3-month visits.

- Hand out subject diary
- Dispense IP supplies for a maximum of 3 months

7. Determination of TGA Parameters and Additional Pre- and Post-Infusion FIX Levels in Standard Cohort Receiving Twice-Weekly Prophylactic Infusions of BAX326

In a subgroup of up to 20 subjects ≥ 12 years of age receiving twice-weekly prophylactic infusions of BAX326, blood samples for determination of TGA parameters concurrent with pre- and post-infusion FIX determination will be performed **during a 6-month period** at the following time points **after having obtained Informed Consent**:

At regular 3-month study visit:

- Initially, ie, at start of the 6-month period
- after 3 months ± 1 week and
- after 6 months ± 1 week of twice-weekly prophylactic infusions

According to the requirements of the 3-month study visits, there will be a wash-out period of at least 5 days (120 h), preferably 7 days. Concurrent with the determination of FIX recovery, pre- and post-infusion blood samples for TGA parameters are also drawn.

FIX activity and TGA parameters will also be determined prior to and following a regular prophylactic infusion at 4 additional time points in a 6-month period, **without the requirement of a wash-out period**:

- On 2 occasions, these should be assessed 3 days after a prophylactic infusion, ie, before and after the subsequent prophylactic infusion of BAX326:
  - Last prophylactic infusion approximately 72 hours (3 days) prior to FIX and TGA determination
  - Within 30 minutes prior to regular prophylactic infusion blood sampling for FIX activity and TGA parameters
  - Administration of regular prophylactic infusion of BAX326
  - 30±5 minutes post-infusion blood sampling for FIX activity and TGA parameters
- On another 2 occasions, these should be assessed 4 days after a prophylactic infusion, ie, before and after the subsequent prophylactic infusion of BAX326
  - Last prophylactic infusion approximately 96 hours (4 days) prior to FIX and TGA determination
  - Within 30 minutes prior to regular prophylactic infusion blood sampling for FIX activity and TGA parameters
  - Administration of regular prophylactic infusion of BAX326
  - 30±5 minutes post-infusion blood sampling for FIX activity and TGA parameters

Table 21.1-1
Flow Diagram of Required Procedures for Baxalta Clinical Study 251001

8. Study Completion/Termination Visit

If the subject has accumulated a total of 100 EDs during the course of Studies 250901/251101 and 251001, or BAX326 is licensed in the subject´s country, whichever occurs last, this will be the subject´s study completion/ termination visit.

The visit must be arranged so that there is a wash-out period of at least 5 days (120 hours), preferably 7 days, from the previous dose of BAX326 and the subject must not be actively bleeding.

Prior to the recovery assessment:

1) Review and discuss subject diary
2) Record AEs
3) Concomitant medication and non-drug therapy use
4) Occurrence of target joints
5) Collect Health Resource Utilization items
6) Physical examination
7) Blood draws for:
    a) Immunology (pre-infusion of IP)
    b) Hematology and clinical chemistry
8) Urine sample for urinalysis
9) Assess HR QoL items pre- or post-infusion of BAX326 including Patient Activity Level
10) Vital signs within 15 minutes of start of infusion
11) **Assessment of FIX recovery (and determination of TGA parameters, if applicable)**
    a) Pre-infusion blood draw for FIX activity (and TGA parameters, if applicable) within 0.5 h of start of infusion
    b) Infusion of 75 ± 5 IU/kg BAX326
    c) Post-infusion blood draw for FIX activity (and TGA parameters, if applicable) at 30 ± 5 minutes
    d) Vital signs at 30 ± 5 minutes and 2 h ± 10 minutes following completion of the infusion

21.2 Schedule of Study Procedures and Assessments

21.2.1 Schedule of Study Procedures and Assessments for Subjects Transitioning from 250901 or 251101

Table 21.2-1
Schedule of Study Procedures and Assessments for Subjects Transitioning from 250901 or 251101

Procedures/Assessments	Screening Visit	Study Visit Week 4 ± 1 [j k]	Study Visits: Every 3 Months ± 1 Week [j]	Study Completion / Termination Visit [l]
Informed consent [a]	X			
Eligibility criteria[r]	X	X	X[r]	
Medical history	X[b]			
Medications and non-drug therapies	X[b]	X	X	X
Physical examination [c]	X[b]		X	X
Occurrence of target joints[n]	X		X[h]	X
Adverse events	X[b]	X	X	X
Laboratories [d]	X[b]	X[m]	X	X
PK study[p]			X[p]	
Vital signs [e]	X	X[m]	X	X
Dispense IP [f]	X[g]	X[o]	X	
Incremental Recovery	X	X[m]	X	X
Hand out subject diary	X	X	X	
Review subject diary		X	X	X
Re-evaluation of prophylactic regimen[q]		X[q]	X[q]	X
HR QoL incl Patient Activity Level [i]			X	X
Health Resource Use			X	X

Continued on next page

Continued

[a] Informed consent must be obtained before starting any other procedure related to the continuation study.
[b] Data to be transcribed from 250901/251101 study completion/termination visit to the screening visit of the continuation study (except for CD4 count, which must be assessed to confirm subject's eligibility).
[c] Includes height and weight at screening and weight at the pre-infusion assessments.
[d] For laboratory assessments, see Table 21.3-1. At all assessments, subjects must not be actively bleeding.
[e] Pulse, respiration, supine blood pressure, and temperature to be assessed within 15 minutes prior to the start of infusion and 30 ± 5 minutes and 2 h ± 10 minutes following infusion.
[f] The treatment with BAX326 will be either a prophylactic treatment twice weekly with 50 IU/kg, OR a modified prophylaxis determined by the investigator, OR a PK-tailored prophylactic administration, OR on-demand treatment.
[g] The Investigational Product at screening visit should be dispensed for the period of 4 weeks ± 1 week.
[h] In transitioning subjects occurrence of target joints will be evaluated and documented every 3 months.
[i] HR QoL will be assessed at every second visit.
[j] For subjects switching back to this continuation study from the surgery study[xxv], the respective visit window may be extended from ± 1 week to ± 2 weeks. Every 3 month visits are calculated from Screening for transitioning subjets.
[k] For subjects receiving a PK-tailored treatment regimen, the study site will call the subjects at 8±1, 17 ±1 and 22±1 weeks after start of treatment to discuss the potential occurrence of bleeding episodes and/or AEs.
[l] Study completion/ termination visit should be performed when BAX326 is licensed in the respective country, or the subject has accumulated approximately 100 EDs to BAX326, whichever occurs last.
[m] Only subjects receiving PK-tailored treatment: After 4 ±1 weeks of start of treatment with a PK tailored treatment regimen. These subjects have two Week 4±1 visits: first visit = regular visit to confirm eligibility; second visit = vist for PK-tailored subset after 4 weeks of start of PK-tailored treatment regimen and 2 months prior to next scheduled 3-month visit.
[n] A target joint is defined as one in which there have been ≥ 4 bleeds in the 6 months prior to study entry or during the last 6-month period being in the study.
[o] Dispense IP supplies for 2 months
[p] Abbreviated PK study will be performed in subjects planned to receive a PK-tailored treatment regimen and who have not participated in a PK study with BAX326 in either BAX326 Pivotal or BAX326 Surgery. It should take place at one of the 3-month study visits.
[q] In subjects receiving a prophylactic treatment (standard, modified or PK-tailored) the regimen needs to be re-evaluated and if needed adjusted. Further guidance is provided under protocol Section 8.6.3.1.
[r] Only CD4 count needs to be assessed every 12 months to confirm subject's eligibility.

[xxv] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

21.2.2 Schedule of Study Procedures and Assessments for Newly Recruited Subjects

Table 21.2-2
Schedule of Study Procedures and Assessments for Newly Recruited Subjects

Procedures/Assessments	Screening Visit	First Infusion (ED1)	Study Visit Week 4 ± 1 [i j]	Study Visits: Every 3 Months ± 1 Week [i]	Study Completion / Termination Visit [k]
Informed consent [a]	X				
Eligibility criteria[o]	X			X[o]	
Medical history	X				
Medications and non-drug therapies	X	X	X	X	X
Physical examination [c]	X	X	X	X	X
Occurrence of target joints[l]	X			X	X
Adverse events		X	X	X	X
Laboratories [d]	X	X	X	X	X
PK Study[b]		X[b]			
Vital signs [e]	X	X	X	X	X
Dispense IP [f]		X[g]	X[n]	X	
Incremental Recovery	X	X	X	X	X
Hand out subject diary	X	X	X	X	
Review subject diary		X	X	X	X
Re-evaluation of prophylactic regimen[m]			X	X[m]	X[m]
HR QoL [h]	X	X		X	X
Health Resource Use	X	X	X	X	X

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Continued

[a] Informed consent must be obtained before starting any other procedure related to the continuation study.
[b] Abbreviated PK study will be performed in those subjects who are planned to receive a PK-tailored dosing regimen. Please refer to Table 21.5-1 for further details on PK assessment.
[c] Includes height and weight at screening and weight at the pre-infusion assessments.
[d] For laboratory assessments, see Table 21.4-1. At all assessments, subjects must not be actively bleeding.
[e] Pulse, respiration, supine blood pressure, and temperature to be assessed within 15 minutes prior to the start of infusion and 30 ± 5 minutes and 2 h ± 10 minutes following infusion.
[f] The treatment with BAX326 will be either a prophylactic treatment twice weekly with 50 IU/kg, OR a modified prophylaxis determined by the investigator, OR a PK-tailored prophylactic treatment regimen.
[g] The Investigational Product at ED1 visit should be dispensed for the period of 4 weeks ± 1 week.
[h] HR QoL including Patient Activity Level will be assessed at every second visit.
[i] For subjects switching back to this continuation study from the surgery study[xxvi], the respective visit window may be extended from ± 1 week to ± 2 weeks.
[j] For subjects receiving a PK-tailored treatment regimen, the study site will call the subjects at 8±1, 17 ±1 and 22±1 weeks after start of treatment to discuss the potential occurrence of bleeding episodes and/or AEs. Every 3 month visits are calculated from the ED1 visit for newly recruited subjects.
[k] Study completion/ termination visit should be performed when BAX326 is licensed in the respective country, or the subject has accumulated a total of 100 EDs to BAX326, whichever occurs last.
[l] A target joint is defined as one in which there have been ≥ 4 bleeds in the 6 months prior to study entry or during the last 6-month period being in the study.
[m] In subjects receiving a prophylactic treatment (standard, modified or PK-tailored) the regimen needs to be re-evaluated and if needed adjusted. Further guidance is provided under protocol Section 8.6.3.1.
[n] Dispense IP supplies for 2 months
[o] Only CD4 count needs to be assessed every 12 months to confirm subject's eligibility.

[xxvi] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

21.3 Clinical Laboratory Assessments for Transitioning Subjects

Table 21.3-1
Clinical Laboratory Assessments for Subjects Transitioning from 250901 or 251101[a]

Assessments	Screening Visit	Study Visit [i] 4 ± 1 Week[j p]	StudyVisits: Every 3 Months ± 1 Week[j]	Study Completion/ Termination Visit[d]
CD4 count	X		X [h]	
HIV test and viral load, if positive	X			X
Pregnancy Test (if applicable)[o]	X		X [n]	
FIX recovery[b]	X	X [p]	X	X
Hematology [c]	X		X	X
Clinical Chemistry [d]	X		X	X
Urinalysis[e]	X		X	X
Immunology[f]	X		X [g]	X [g]
Abbreviated PK for subjects not having performed a PK in BAX326 Pivotal or BAX326 Surgery			X [k l]	
TGA parameters, if applicable [m]		X [m]	X [m]	X [m]
Prothrombotic markers [o]				

[a] At all assessments, subjects must not be actively bleeding. In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated.
[b] For assessment of recovery: samples will be taken within 0.5 h before the start of the infusion, and at 0.5 h ± 5 minutes after the infusion. The washout period of at least 5 days (120 h), preferably 7 days, is necessary.
[c] Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.
[d] Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose.
[e] Urinalysis assessment: protein. Urinalysis should also be performed if inhibitors are detected.

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[f] Immunology assessments include: total binding and inhibitory antibodies to FIX, and antibodies to CHO protein and rFurin. If an inhibitory antibody with a Nijmegen titer ≥ 0.6 BU or total binding antibodies with a positive titer of 1:80 is detected, the test will be confirmed in the central laboratory within 2 weeks of study site notification. In either case the following additional tests will be performed: IgA, IgM, IgG subtypes, and hs-CRP; additional markers may be tested if applicable. If an inhibitor is suspected there may be additional testing for lupus anticoagulans/phospholipid antibodies, or FIX antibody testing with a different methodology. If a subject develops a severe allergic reaction or anaphylaxis the following tests will be performed: hs-CRP, CIC-C1q and CIC-C3 for circulating immune complexes, and IgE. Furthermore, Ig subtypes, inhibitory and total binding antibodies.

[g] Immunology testing to be performed at least 3 days (72 h) after the previous infusion of BAX326 and before IP is administered at this visit.

[h] CD4 count will be assessed at screening and then every 12 months to confirm the subject's eligibility.

[i] At the confirmatory visit in 4 weeks ± 1 week from screening, the eligibility should be confirmed using the lab results.

[j] For subjects switching back to this continuation study from the surgery study[xxvii], the respective visit window may be extended from ± 1 week to ± 2 weeks. Every 3 month visits are calculated from Screening for transitioning subjets.

[k] Applicable only for subjects receiving a PK-tailored treatment regimen.

[l] For a detailed schedule, see Section 21.5.

[m] Only in subjects ≥ 12 years of age. For details see Section 11.2 TGA testing

[n] Pregnancy test as appropriate, and to be repeated during the course of the study in countries where mandated by national law.

[o] Prothrombotic markers: TAT complexes, D-dimers, Prothrombin fragment 1.2. Prothrombin markers should also be determined whenever clinically indicated.

[p] Only applicable to subjects receiving PK-tailored treatment: After 4 ±1 weeks of start of treatment with a PK tailored treatment regimen. These subjects have two Week 4±1 visits: first visit = regular visit to confirm eligibility; second visit = vist for PK-tailored subset after 4 weeks of start of PK-tailored treatment regimen and 2 months prior to next scheduled 3-month visit.

[xxvii] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

21.4 Clinical Laboratory Assessments for Newly Recruited Subjects

Table 21.4-1
Clinical Laboratory Assessments for Newly Recruited Subjects[a]

Assessments	Screening Visit	First Infusion (ED1)	Study Visit 4 ± 1 Week	StudyVisits: Every 3 Months ± 1 Week[j]	Study Completion/ Termination Visit[d]
CD4 count	X			X[i]	
HIV test and viral load, if positive	X				X
Genetics and HLA-genotype	X[o]				
Pregnancy Test (if applicable) [m]	X			X	X
FIX activity	X				
FIX antigen	X				
FIX recovery[b]		X	X[k]	X	X
Abbreviated PK[k]		(X)	(X)	(X)	
Hematology [c]	X		X	X	X
Clinical Chemistry [d]	X		X	X	X
Urinalysis[e]	X		X	X	X
Immunology[f]	X	X[g]	X[h]	X[h]	X[h]
Hepatitis serology	X				
INR	X				
TGA[l]		X	X	X	X
Prothrombotic markers[n]	X				

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[a] At all assessments, subjects must not be actively bleeding. In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated.

[b] For assessment of recovery: samples will be taken within 0.5 h before the start of the infusion, and at 0.5 h ± 5 minutes after the infusion. The washout period of at least 5 days (120 h), preferably 7 days, is necessary.

[c] Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.

[d] Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose.

[e] Urinalysis assessment: protein. Urinalysis should also be performed if inhibitors are detected.

[f] Immunology assessments include: total binding and inhibitory antibodies to FIX, and antibodies to CHO protein and rFurin. If an inhibitory antibody with a Nijmegen titer ≥ 0.6 BU or total binding antibodies with a positive titer of 1:80 is detected, the test will be confirmed in the central laboratory within 2 weeks of study site notification. In either case the following additional tests will be performed: IgA, IgM, IgG subtypes, and hs-CRP; additional markers may be tested if applicable. If an inhibitor is suspected there may be additional testing for lupus anticoagulans/phospholipid antibodies, or FIX antibody testing with a different methodology. If a subject develops a severe allergic reaction or anaphylaxis the following tests will be performed: hs-CRP, CIC-C1q and CIC-C3 for circulating immune complexes, and IgE. Furthermore, Ig subtypes, inhibitory and total binding antibodies.

[g] Immunology testing to be performed prior to the first infusion of BAX326 at ED1 or PK, if performed at ED1.

[h] Immunology testing to be performed at least 3 days (72 h) after the previous infusion of BAX326 and before IP is administered at this visit.

[i] CD4 count will be assessed at screening and then every 12 months to confirm the subject's eligibility.

[j] For subjects switching back to this continuation study from the surgery study[xxviii], the respective visit window may be extended from ± 1 week to ± 2 weeks. Every 3 month visits are calculated from the ED1 visit for newly recruited subjects.

[k] Abbreviated PK for FIX and TGA parameters (if subjects ≥ years of age) only in those subjects who are planned to receive a PK tailored treatment regimen. The PK can be performed at any study visit once eligibility is confirmed. A detailed schedule can be found under Section 21.5.

[l] To be performed only in subjects ≥ 12 years of age. For details see Section 11.2 TGA Testing.

[m] Pregnancy test as appropriate, and to be repeated during the course of the study in countries where mandated by national law.

[n] Prothrombotic markers: TAT complexes, D-dimers, Prothrombin fragment 1.2. Prothrombin markers should also be determined whenever clinically indicated.

[o] If results of FIX gene mutation analysis and HLA genotype are already available at the study site, they will be provided to the sponsor and an additional analysis will not be required.

[xxviii] Surgery Study 251002 was completed in May 2014. Thirty unique subjects underwent 38 surgeries.

21.5 Abbreviated PK Study for Subjects Receiving PK-Tailored Prophylaxis (if newly recruited subjects or PK evaluation not done in BAX 326 Pivotal or BAX326 Surgery)

Table 21.5-1
Abbreviated PK Study[b]

Procedure/ Assessment	Within 0.5 hours Pre-Infusion	BAX326 Infusion	30 ± 5 Min Post-infusion	9 ± 3 hours Post-infusion	24 ± 6 hours Post-infusion	48 ± 6 hours Post-infusion	72 (- 6) hours Post-infusion
FIX activity	X		X	X	X	X	X
TGA parameters[a]	X		X	X	X	X	X
Infusion of BAX326, at dose of 75 ±5 IU/kg		X					

[a] TGA parameters: lag time, time to peak thrombin generation, peak thrombin generation, and ETP, only to be performed in subjects ≥ 12 years of age

[b] Assessment must be performed at least 5 days (120 hours), preferably 7 days, following the previous dose of a FIX product and the subject must not actively bleed and eligibility must be confirmed.

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SUMMARY OF CHANGES

BAX 326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study

Short Title: BAX326 Continuation

PROTOCOL NUMBER: 251001

AMENDMENT 6 VERSION: 2015 OCT 19

In this section, changes from the previous global version of the Protocol, Amendment 5, dated 2015 Mar 19, will be described and their rationale will be given.

1. ***Throughout the Document***

   Minor grammatical and/or administrative changes have been made to improve the readability and/or clarity of the protocol.

   For references to BAX326 Surgery Study 251002 appropriate text or footnotes have been added to make it clear that Surgery Study 251002 was completed in May 2014.

2. ***Section 1 Study Personnel***

   The information in this section was aligned with the current protocol template (version 2015 Apr 20).

3. ***Section 2 Serious Adverse Event Reporting***

   This section was aligned with the current protocol template (version 2015 Apr 20).

4. ***Section 3 Synopsis: Planned Study Period***
   Section 3 Synopsis: Planned Duration of Subject Participation
   Section 6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects
   Section 7.1 Study Purpose
   Section 8.1 Overall Study Design
   Section 8.1.1 Newly Recruited Subjects
   Section 8.2 Duration of Study Period(s) and Subject Participation

   Description of changes: The maximum study duration per subject was increased from 57 to 68 months. The study completion date was changed from Q4 2015 to Q4 2016. The end of study participation is defined by receiving a product license in the respective country and accumulation of 100 EDs. The end date for subject participation was limited to December 31, 2016 : "*... but no later than December 31, 2016."* However, if a limited number of newly recruited subjects have not have reached 100 EDs by Dec 31, 2016, these may continue until they have reached approximately 100 EDs.

   Reason for changes: According to regulatory authority request, at least 25 additional, BAX326 naïve patients will be enrolled and treated, which is the reason for the study prolongation.

5. ***Section 3 Synopsis: Health Related Quality of Life, Patient Activity Level and Pharmacoeconomic Parameters***
   Section 8.3.2.4 Health related Quality of Life, Patient Activity Level and Health Resource Use
   Section 13.2 Assessment of Health-related Quality of Life and Health Resource Use

   Description of changes: Clarification was provided regarding which age-specific HRQoL measures and questionnaires are applicable at what time to which subject age.

   Reason for changes: Due to the addition of Cohort 2 (newly recruited, BAX326 naïve subjects), there was a need for clarifying when the Cohort 2 subjects are to be assigned to the age-specific HRQoL measures and questionnaires.

6. ***Section 3 Synopsis: Exploratory Outcome Measures***
   Section 8.3.2.5 Exploratory Outcome Measures
   Section 11.1.5 Additional Determination of Incremental Recovery in Subjects Receiving Modified or PK-Tailored Prophylaxis

   Description of changes: The text defining the number of subjects in whom TGA parameters will be determined as an exploratory outcome measure has been deleted. It was clarified that TGA parameters pre- and post-infusion concurrent with IR determination for FIX activity will be investigated in a subset of subjects receiving twice-weekly standard or modified prophylaxis including PK-tailored prophylaxis with BAX326 as well as at some selected timepoints during prophylactic treatment.

   Reason for changes: Since TGA testing is optional and the assignment of the treatment regimen is at the discretion of the investigatorn, it cannot be anticipated that a specific number of subjects under a certain treatment regimen will participate in the TGA testing. These circumstances are considered acceptable since the purpose of TGA testing is merely exploratory.

7. ***Section 3 Synopsis: Subject Selection, Planned Number of Subjects***
   Section 6.3 Population to be Studied
   Section 9.1 Inclusion Criteria & Section 9.2 Exclusion Criteria
   Section 10.3 Screening and Study Visits

   Description of changes: Text describing the addition of at least 25 BAX326 naïve subjects with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) hemophilia B has been added. The term “Cohort 1” was introduced for subjects who were previously treated in BAX326 Studies 250901 or 251101 before enrollment in Study 251001. The term “Cohort 2” was introduced for newly recruited, BAX326 naïve subjects.

   Reason for changes: For easier readability when explaining differences of protocol requirements for previously treated subjects and BAX326 naïve subjects.

8. Section 3: Synopsis: Investigational Product

Description of change: Addition of the following type of treatment: Individual subject treatment and dosing for IR during the optional additional visits for subjects under standard or modified prophylaxis.

Reason for change: This text was inserted since the purpose of IR assessment at additional visits was to assess the IR at doses that are normally administered for an individual subject´s prophylactic treatment. Therefore, the doses administered at these visits will vary from subject to subject and will depend on the individual subject´s prophylactic treatment dose.

9. Section 6.4 Findings from Nonclinical and Clinical Studies, Section 6.4.2: Phase 3 Surgery Study

Description of changes: The previous description of the BAX326 surgery study, which was based on the interim clinical study report (October 2012), was updated with the data of the final clinical study report (October 2014). Table 6.4-1 was replaced with the final hemostatic efficacy data.

Reason for the changes: Update of clinical study data due to completion of study and availability of final clinical study report.

10. Section 6.5: Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Description of changes: This section has been updated based on the most recent ISS (Integrated Analysis of Safety, data cut-off: June 2013) and the final results of the Surgery Study 251002.

Reasons for changes: Clinical study data update to reflect the most most recent safety and efficacy results.

11. Section 8.1 Overall Study Design
Section 8.1.2 Subjects Receiving PK-tailored Prophylaxis
Table 21.1-1, item 4c: Study Visit Week 4±1 in Subjects who are Not Newly Recruited and who Receive a PK-Tailored Dosing Regimen (4±1 week after start of PK tailored treatment)
Table 21.1-1, item 5: PK-Tailored Dosing

Description of changes/reasons for changes:

1) As the surgery study has been completed, information has been added regarding the need for sponsor approval for all surgeries. If approval is not given by the sponsor for a surgery to be performed in a subject during participation in 251001, the respective subject will be withdrawn from further study participation.
2) The section has been revised and new text has been added regarding the PK-tailored prophylactic treatment regimen to define the start time and subsequent visits for the PK-tailored treatment regimen.
3) The text regarding the timepoints for determination of FIX activity and TGA parameters has been updated for more clarity.

12. Section 3 Synopsis: Investigational Product
Section 8.1.2 Newly Recruited Subjects
Section 8.1.3 Subjects Receiving PK-tailored Prophylaxis
Section 8.6.3.1 Prophylactic Treatment
Section 8.6.3.1.1 PK-Tailored Prophylaxis
Section 14.3.2.2 Pharmacokinetics

Description of change: A maximum dose of 120 IU/kg was introduced for PK-tailored prophylaxis. The following text was added: "The maximum dose is 120 IU/kg. Doses higher than 120 IU/kg are not allowed and therefore frequencies requiring a higher dose are excluded."

Reason for change: An increased dose of up to 120 IU/kg is allowed for patients receiving PK-tailored prophylaxis to allow patients with poor incremental recoveries to continue on a regimen of twice weekly dosing while maintaining factor IX levels of > 1% (>1 IU/dL). This reflects the variability in half-lives and incremental recovery in patients with factor IX deficiency. In studies of BAX326 the lower range of half-life and incremental recovery was 15.24 hours and 0.5, respectively. Accordingly, some additional flexibility for higher doses than 120 IU/kg is added to the protocol to reflect current standard of care.[i]

[i] Björkman, S. Population pharmacokinetics of recombinant factor IX: implications for dose tailoring. Haemophilia. 2013 Sep;19(5):753-7.

13. Section 8.5 Study Stopping Rules
Section 12.9 Data Monitoring Committee

Description of changes:

1) The previous name "Data Safety Monitoring Committee (DSMC)" was changed to "Data Monitoring Committee (DMC)".

2) The review of SAEs by the DMC chair will be stopped as of the beginning of 2016.

Reason for changes:

1) To reflect the language of the current protocol template (version 2015 Apr 20).

2) Subjects in Cohort 1 have accumulated at least 100 EDs; many of them have received treatment for much longer, due to the fact that BAX326 was not yet licensed in the respective countries, which, according to the study protocol, was a prerequisite for completion of study participation, provided that the 100 EDs were fulfilled. During this prolonged time period all safety-relevant datawere continuously reviewed by the DMC, without identifying any safety concern. Furthermore, because BAX326 is now marketed in several countries (trade name: Rixubis), the post-marketing safety reporting system is now more important for ensuring safety for patients in the trial and provides more extensive coverage of safety than review of trial SAEs. Of course, the sponsor will report any relevant safety events to trial investigators.

14. Section 8.6 Investigational Product, Section 8.6.2: Administration

Description of change: Addition of a sentence explaining that partial (ie, not whole) vials may be used in minor subjects < 12 years of age for Incremental Recovery or PK determination as described in Section 8.6.3.1.1 or for other infusions for subjects not older than 5 years of age only upon agreement with Baxalta.

Reason for change:
The text that partial vials may be used for IR or PK assessment in subjects < 12 years of age has been added to be consistent with Section 8.6.3.1.1. The introduction of the use of partial vials in subjects younger than 6 years upon agreement with the sponsor is due to the express wish of a few investigators, as this allows a more exact dosing.

15. Section 8.7 Investigational Product Accountability

This section was aligned with the current protocol template (version 2015 Apr 20).

16. Section 8.8 Source Data

Description of change: The section heading (previously named "Data Recorded Directly on Case Report Forms") was renamed "Source Data" and text was added.

Reason for change: To reflect the language of the current protocol template (version 2015 Apr 20).

17. Section 3 Synopsis:Statistical Analysis
Section 14.2 Datasets and Analysis Cohorts

Description of changes:

1) A sentence was added to clarify that for subject who discontinue before reaching 100 exposure days (EDs), data will be included up through the day of discontinuation. The FAS will be used for all analyses.
2) The statement regarding the FAS was added to the statistical analysis section in the synopsis.

Reason for changes:

1) There was a need for clarification that for subjects who discontinue before reaching 100 EDs, data will be included up through the day of discontinuation. The FAS will be used for all analyses.
2) Consistency

18. Section 3 Synopsis:Statistical Analysis
Section 14.3 Methods of Analysis

Description of change: A sentence was added to clarify that safety and efficacy data from the additional BAX326 naïve subjects (Cohort 2) will be analyzed together with the data from the previously treated subjects (Cohort 1).

Reason for change: Due to the addition of Cohort 2 (newly recruited BAX326 naïve subjects), there was a need for clarification that the safety and efficacy data from the additional BAX326 naïve subjects will be analyzed together with the data from the previously treated subjects (Cohort 1).

19. Section 9.3 Withdrawal and Discontinuation

Description of changes:

1) The sentence regarding ALT/AST levels in subjects with chronic hepatitis B or C has been updated in order to allow a repeat testing.
2) A bullet point has been added to the reasons for subject discontinuation: "The subject requires major surgery which will be performed outside the scope of the surgery study (e.g site not participating in surgery study, surgery study completed)"

Reason for changes:

1) The sentence has been added since ALT/AST levels exceeding 5 times the upper limit of normal would not lead to the exclusion of a subject in case a retest showed decreased results within the allowed ranges for ALT/AST.
2) As the surgery study has been completed, subjects requiring major surgeries have to be discontinued.

20. Section 10.5 Subject Diary

Description of change: Information was added that subjects and/or their legally authorized representatives will be trained on the use of the diary, and that the subject diary will serve as a source record and remain at the study site.

Reason for change: To reflect the language of the current protocol template (version date 2015 Apr 20).

21. Section 11 Assessment of Efficacy, Section 11.1 Determination of FIX Activity Section 21.1 Flow Diagram of Study Procedures Section 21.4: Clinical Laboratory Assessments

Description of changes:

1) The second bullet point regarding the vial potency to be used for subjects <12 years of age has been updated (addition in italics): "In subjects < 12 years of age, the total calculated dose should not be rounded up or down to the nearest whole vial *in case a dose of 75 ± 5 IU/kg cannot be reached."*

2) One bullet point has been added regarding the total dose and vial potency to be used for the IR determination during optional additional visits for subjects receiving standard or modified prophylaxis: The individual subject´s treatment and dosing regimen will be used for IR determination during the optional additional visits. The total dose and potency of the vials used for IR determination will be consistent with the vials used for routine (home) treatment (ie, any potency may be administered).

Reason for changes:

1) To clarify that partial vials may be used for FIX activity testing in subjects < 12 years of age, as also clarified in Sections 8.6.2 and 8.6.3.1.1.

2) This bullet point was added since the purpose of IR assessment at additional visits was to assess the IR at doses that are normally administered for an individual subject´s prophylactic treatment. Therefore, the doses administered at these visits will vary from subject to subject and will depend on the individual subject´s prophylactic treatment dose.

22. Section 11.1.5 Additional Determination of Incremental Recovery in Subjects Receiving Modified or PK-Tailored Prophylaxis

Description of change: The additional IR determination in subjects <12 years of age has been changed from "optional" to "not required".

Reason for change: This sentence was added to clarify that it is not expected in this study that subjects < 12 years of age will participate in the additional optional visits. The optional visits are only applicable in case a subject will participate in TGA testing. Since TGA testing is not an option for subjects < 12 years of age, these subjects will not have any optional additional visits.

23. Section 11.2.3 Additional Determination of TGA Parameters in Subjects Receiving Modified Prophylaxis

Description of changes:

1) The additional determination of TGA parameters will be performed in subjects receiving modified prophylaxis only and not in subjects on PK tailored prophylaxis anymore.

2) The previously 2-6 timepoints for the TGA parameter determination have been changed to 4 timepoints.

Reason for changes:

1) The text was revised to make it clear that no additional visits are planned for subjects under PK-tailored treatment, since it is expected that these subjects will receive the PK-tailored dose only once per week. Therefore, it will not be necessary to conduct unscheduled visits at other timepoints than the regular study visits where the subjects will attend the site for an infusion after a 7-day wash-out period that will comply with their regular interval prior to a routine (home treatment) infusion.

2) Four different timepoints will capture all relevant options for TGA testing.

24. Section 12 Assessment of Safety

This section was revised slightly and the subsections were renumbered to be consistent with the current protocol template (version 2015 Apr 20).

25. Section 12.1.2.2 Causality

Description of change: The sentence "For each AE assessed as 'not related/associated' or 'unlikely related/associated', the investigator shall provide an alternative etiology" was revised as follows: 'For each **SAE** assessed as 'not related/associated' or 'unlikely related/associated', the investigator shall provide an alternative etiology **on the SAE form**.'

Reason for change: As the question regarding the alternative etiology for AEs is not in the AE CRF for this study[ii], this requirement was modified and made applicable for SAEs only.

[ii] This requirement was not in the protocol template or standard CRF at the time of study start. When this requirement was added in 2013, a note to file was prepared by the medical director in 2013 to document that the alternative etiology for AEs assessed as not related or unlikely related would not be collected in this study.

26. Section 18.2 Study Documents and Case Report Forms

This section was aligned with the current protocol template (version 2015 Apr 20).

27. Section 21 Study Flow Chart

The study flow chart (previously in Section 21.1) was removed due to the complexity of the study. The flow diagram in Section 21.1 replaces the study flow chart.

28. Table 21.1-1 Flow Diagram of Required Procedures
Table 21.2-1 Schedule of Study Procedures and Assessments for Subjects Transitioning from 250901 or 251101
Table 21.2-2 Schedule of Study Procedures and Assessments for Newly Recruited Subjects
Table 21.3-1 Clinical Laboratory Assessments for Subjects Transitioning from 250901 or 251101

Description of change: Clarification added in footnote j: Every 3 month visits are calculated from the ED1 visit for newly recruited subjects. Every 3 month visits are calculated from Screening for transitioning subjets.

SUMMARY OF CHANGES

BAX 326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study

Short Title: BAX326 Continuation

PROTOCOL NUMBER: 251001

AMENDMENT 5 VERSION: 19 March 2015

In this section, changes from the previous global version of the Protocol, Amendment 4, dated 31 July 2013, will be described and their rationale will be given.

1. Throughout the Document

Description of Change: Change of sponsor name/entity
Purpose for Change: Administrative.

SUMMARY OF CHANGES

BAX 326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B – A Continuation Study

Short Title: BAX326 Continuation

PROTOCOL NUMBER: 251001

AMENDMENT 4 VERSION: 31 July 2013

In this section, changes from the previous global version of the Protocol, Amendment 2, dated 07 December 2011[i], will be described and their rationale will be given.

1. Throughout the Document

Minor grammatical and/or administrative changes have been made to improve the readability and/or clarity of the protocol.

2. Protocol Title

Section 3 Synopsis: Clinical Conditions/Indications, Protocol Title, Study Design, Inclusion Criteria for Newly Recruited Subjects
Section 8.1 Study Design
Section 9.1.2 Inclusion Criteria for Newly Recruited Subjects

Description of change:
The definition of 'moderately severe' hemophilia B was changed from ≤2% to 1-2%.

Reason for change:
Clarification and consistency with other BAX326 documents.

[i] Amendment 3 (version date 28 December 2011) is a regional amendment specific to the UK.

3. *Section 1: Study Personnel*

Description of change:
Details of Authorized Representative (Signatory) changed and Sponsor's Medical Expert deleted.

Reason for change:
To comply with revised protocol template.

4. *Section 2: Serious Adverse Event Reporting*

Description of change:
Details of fax number and e-mail address for SAE reporting amended for all study sites (PPD /PPD).

Reason for change:
To comply with revised and upcoming protocol template.

5. *Section 6.1: Description of Investigational Product*
Section 6.4: Findings from Nonclinical and Clinical Studies
Section 6.5: Evaluation of Anticipated Risks and Benefits of the Investigational product(s) to Human Subjects

Description of changes:

1) Findings from clinical studies updated with results from pivotal study (250901), interim data from the surgery study (251002) as well as safety data from the Integrated Safety Summary (ISS) with a data-cut of 3 September 2012.
2) Information on BeneFIX shortened.
3) Number of additional BAX326 studies changed from 4 to 3.

Reason for changes:

1) New data have become available since the last amendment. The findings have not altered the risk/benefit ratio of BAX326. Overall, the BAX326 data showed a PK profile comparable to BeneFIX and an acceptable safety and efficacy profile in various clinical settings in different age ranges including peri-operative management.
2) Information on BeneFIX shortened, as clinical data are now available for BAX 326.
3) No PUP study with BAX326 will be necessary based on new EMA guideline EMA/CHMP/BPWB/144552/2009, effective as of 1 February 2012.

6. ***Section 3 Synopsis: Objectives***
   Section 3 Synopsis: Outcome MeasureHealth Related Quality of Life and Pharmacoeconomic parameters
   Section 3 Synopsis: Statistical Analysis
   Section 7.2 Study Objectives
   Section 8.3.2.4 Health related Quality of Life and Health Resource Use
   Section 13 Assessment of Health-related Quality of Life
   Section 14.3.2.4 Statistical Analysis

   Description of changes:

   1) The assessment of the Patient Activity Level was added.
   2) The analysis of the patient activity level will be descpritive in nature.

   Reason for changes:

   1) To determine the Patient Activity Level in hemophilia B subjects and changes over time.
   2) To describe the statistical evaluation.

7. ***Section 3: Synopsis Planned Study Period***
   Section 3: Synopsis Planned Duration of Subject Participation
   Section 8.2 Duration of Study Period(s) and Subject Participation

   Description of changes:

   1) The completion of the study is anticipated to be Q4 2015 instead of Q1 2015 with a respective prolongation of the duration from approximately 48 to 57 months.
   2) The planned subject participation for newly recruited subjects is defined.

   Reason for changes:

   1) To take new regulatory requirements for licensure of new products in some participating countries into account.
   2) To define the time period of study participation for newly recruited subjects.

8. Section 3: Synopsis Investigational Product
Section 6.1: Description of Investigational Product

Description of changes:

1) Addition of PK-tailored prophylactic administration of BAX326 as an additional prophylactic treatment option and the rationale provided.
2) It is clarified that newly recruited subjects have to receive prophylactic treatment.

Reason for changes:

1) The PK-tailored treatment regimen which is based on the subject's individual PK ensures that FIX levels of at least 1% above the subject's individual baseline are maintained which should minimize the number of bleeding episodes. The targeted FIX trough level may need to be higher depending on the subject's bleeding phenotype, joint status and/or physical activity.
2) To ensure that subjects will receive the required number of EDs to BAX326 within the study period.

9. Section 3 Synopsis: Statistical Analysis
Section 14.1 Sample size and Power Calculations
Section 14.4 Planned Safety Review

Description of change:

1) Added information that the sample size calculation also depends on regulatory requirements.
2) An interim safety review may be performed when at least 50 subjects have accumulated at least 100 EDs to BAX 326.

Reason for change:

1) To describe the rationale for the additional 25 subjects to be newly recruited.
2) To ensure a timely evaluation of long-term efficacy and safety data of 50% of subjects in light of the fact that the LSO is anticipated to be Q4 2015 instead of Q1 2015.

10. Section 6.1: Description of Investigational Product
Section 8.6.3.2: Treatment of Bleeding Episodes

Description of changes:

1) Required units recalculated due to revised Incremental Recovery (IR) (from 0.8 to 0.9) in subjects ≥ 12 years of age. Text changed to: 'body weight (kg) x desired FIX rise (% or (IU/dL)) x **1.1** IU/kg' (previously 1.3 IU/kg).
2) It was highlighted that due to large inter-individual and age related differences in IR the dose should be individually tailored.

Reason for changes:

1) The IR was revised based on the PK data of BAX326 pivotal protocol 250901.
2) To emphasize that the large inter-individual and age-related differences in IR are taken into account to ensure a correct dose.

11. Section 3 Synopsis: Study Purpose
Section 3 Synopsis: Study Design
Section 3 Synopsis: Planned Duration of Subject Participation
Section 3 Synopsis: Planned Number of Subjects
Section 6.3: Population to be Studied
Section 8.2: Duration of Study Period(s) and Subject Participation
Section 21.2: Flow Diagram of Study Procedures
Section 21.3: Schedule of Study Procedures and Assessments

Description of change:

At least 25 subjects naïve to BAX326 will be newly recruited.

Reason for change:

To comply with regulatory requirements, ie, to obtain long-term efficacy and safety data in approximately 100 PTPs aged 2-70 years who have accumulated up to approximately 100 EDs to BAX326.

12. Section 3 Synopsis: Study Purpose
Section 7.1: Study Purpose

Description of change:

The wording of the study purpose was revised and hemostatic efficacy listed as second objective. Also, newly recruited subjects will be added to the total study population and the overall duration of subject's study participation is defined.

Reason for change:

To be consistent with the order of objectives as described in Section 7.2 and Outcome Measures described in Section 8.3 and to highlight that also newly recruited subjects will be added to the total study population.

13. Section 3 Synopsis: Study Purpose and Objectives
Section 3 Synopsis: Outcome Measures
Section 7.1: Study Purpose
Section 7.2: Study Objectives
Section 3 Synopsis: Outcome Measures
Section 8.3: Outcome Measures

Description of changes:

1) The order of the objectives in the synopsis was rearranged to be consistent with the objectives in the main body of the protocol and to match the order of the outcome measures.
2) It is highlighted that the hemostatic efficacy of the various prophylactic dose regimens in the prevention of acute bleeding episodes will be evaluated.
3) The order of the study objectives and outcome measures was rearranged. Hemostatic efficacy is listed now as the first secondary outcome measure.
4) The pharmacokinetic parameters have been added as an additional outcome measure.
5) An additional exploratory objective was added: 'To correlate pre-infusion TGA parameters with pre-infusion FIX levels and spontaneous breakthrough bleeds while receiving PK-tailored, once-weekly prophylactic treatment and in up to 20 subjects receiving standard prophylactic treatment'

Reason for changes:

1) To improve consistency and clarity.
2) To take the various prophylactic treatment options into account.
3) To comply with regulatory request.
4) To take the additional PK-tailored prophylactic treatment regimen into account.
5) To evaluate whether and which TGA parameters, in particular ETP and/or peak thrombin generation may be a better parameter to monitor the adequacy of prophylactic treatment instead of FIX activity trough levels and/or clinical outcome.

14. Section 8.1: Overall Study Design
Section 21.1: Study Flow Chart
Section 21.2: Flow Diagram of Study Procedures
Section 21.3: Schedule of Study Procedures and Assessments
Section 21.4: Clinical Laboratory Assessments

Description of changes:

1) At least 25 subjects not previously exposed to BAX326 are newly recruited and the respective procedures described. Other subjects are classed as "subjects transitioning from BAX326 Pivotal or BAX326 Pediatric Study". It is also highlighted that newly recruited subjects may only receive prophylactic treatment.
2) New text and procedures added regarding PK-tailored prophylactic treatment regimen which constitutes an additional prophylactic treatment option.
3) TGA testing will be done in approximately 20 subjects ≥ 12 years of age receiving standard twice-weekly prophylactic infusions, and in all subjects ≥ 12 years of age receiving modified or PK-tailored prophylactic infusions of BAX 326 as follows: determination of TGA parameters pre- and post-infusion concurrent with IR for FIX over 6 months at their regular 3-month visit, in total 3 times. In addition, TGA parameters will be determined at the following timepoints:

   Standard twice-weekly prophylactic infusions: In approximately 20 subjects at 4 different time points within this 6-month period pre- and postinfusion TGA parameters and FIX activity level will be determined. On 2 occasions these should be assessed 3 days after a prophylactic infusion, ie, immediately before and after the next prophylactic infusion of BAX 326, and on the other 2 occasions 4 days after a prophylactic infusion, ie, immediately before and after the next prophylactic infusion of BAX 326.

   Modified and PK-tailored prophylactic infusions: In all subjects, TGA parameters and FIX activity level will also be determined within a 6-month period pre- and postinfusion at different timepoints depending on the frequency of weekly prophylactic infusions . The pre- and post-infusion blood draws should occur such, that 2 occasions always reflect one dosing interval.

Reason for changes:

1) To comply with a regulatory request.
2) To provide procedures for the PK-tailored prophylactic treatment regimen.
3) To describe the timeponts of the determination of TGA parameters in a subset of subjects ≥ 12 years of age.

15. Section 8.1: Overall Study Design
Section 8.6.3.3 Description of Treatment: Surgery

Description of changes:

1) The text regarding elective or emergency surgery was moved to the beginning.
2) It is emphasized that the subject "has to be temporarily transitioned…" to the surgery study instead of "… can be temporarily..".
3) To highlight the section regarding surgery a respective title was added.

Reason for change:

1) This text is applicable to all subjects irrespective of their treatment.
2) To clarify that surgeries are not allowed in the Continuation study.
3) To emphasize the need that subjects have to be transitioned to the surgery study in case a surgery is required.

16. Section 6.1: Description of Investigational Product
Section 8.1: Overall Study Design
Section 8.6.3 Description of Treatment

Description of change:

In the sentence "Subjects participating in the BAX326 pivotal, continuation or pediatric study may/can be transitioned to BAX326 surgery study to undergo surgery" the option 'may/can' has been changed to a compulsory 'have to be transitioned". Exemptions may be granted for minor interventions in case the surgery study is not in place at a study site.

Reason for change:

To ensure that the subject is transitioned to the surgery study to receive BAX326 according to the protocol prescribed treatment regimen. Otherwise, subjects have to exit the BAX326 program.

17. Section 8.6.1Packaging, Labeling, Reconstitution, Storage, and Shelf-life

Description of changes:

1) 250 and 3000 IU vials have been added. The sentence that these potencies will be added during the trial was removed.
2) Vials from different lots/infusion may be used, preferably not more than two different lots/infusion.

Reason for changes:

1) The 250 and 3000 IU potency vials have in the meantime become available.
2) To provide more flexibility.

18. Section 8.6.1 Packaging, Labeling, Reconstitution, Storage, and Shelf-Life

Description of change:

Information was added that for an individual subject, study product from only one lot/infusion with a nominal potency of 500 IU/vial was allowed for the abbreviated PK assessment, and not only for IR. The sentence was also highlighted for emphasis.

Reason for change:

To ensure that only 500 IU potency vials are used for any PK determination, ie, for IR and abbreviated PK.

19. Section 8.1.3: PK-Tailored Prophylactic Treatment Regimen
Section 21.2: Flow Diagram of Study Procedures
Section 21.3: Schedule of Study Procedures and Assessments for Subjects Transitioning from 250901 or 251101
Section 21.4: Clinical Laboratory Assessments for Newly Recruited Subjects

Description of change:

A new section was added describing the study design relating to subjects receiving a PK-tailored prophylactic treatment regimen. In summary, newly recruited subjects or subjects transitioning from either the BAX326 pivotal or BAX326 pediatric study can receive PK-tailored prophylaxis. If no PK data are available, these subjects will undergo an abbreviated PK evaluation. Based on the PK results, a dose will be calculated to maintain FIX activity levels in plasma of 1% above the subject's individual FIX level observed at baseline. It is expected that the most common frequency will be twice weekly.

Reason for change:

The PK-tailored treatment regimen which is based on the subject's individual PK ensures that FIX level of at least 1% above the subject's individual baseline, are maintained. This level is generally considered as a protective level against bleeding episodes. However, the targeted FIX trough level may need to be higher depending on the subject's bleeding phenotype, joint status and/or physical activity.

20. Section 3 Synopsis: Outcome Measures, Statistical Analysis
Section 8.1 Study Design
Section 8.3 and subsections: Outcome Measures
Section 14.3 and subsections: Methods of Analysis

Description of changes:

1) PK parameters added to the PK outcome measures section (for subjects receiving a PK-tailored dosing regimen who have not participated in PK assessments in previous BAX326 studies): $AUC_{0\text{-}72\ h}$/dose (area under the plasma concentration versus time curve from 0 to 72 hours post-infusion), $AUC_{0\text{-}\infty}$ /dose (area under the plasma concentration/time curve from time 0 to infinity), IR, T1/2 (elimination phase half-life), MRT (mean residence time), CL (clearance), V_{ss} (Volume of distribution at steady state). Description provided how the PK parameters will be calculated based on an abbreviated blood sampling schedule using a non-linear mixed effect model approach.
2) New exploratory outcome measures added:
   a) Determination of TGA parameters over 72 hours (lag time, time to peak thrombin generation, peak thrombin generation, endogenous thrombin potential [ETP]) and
   b) Determination of TGA parameters concurrent with FIX activity levels in a 6-month period at each study visit as well as at 4-6 different timepoints reflecting the different dose intervals of various prophylactic treatment regimen without requiring a wash-out period. These assessments will be performed in approximately 20 subjects ≥ 12 years receiving twice weekly standard prophylaxis and in all subjects ≥ 12 years, or approximately 20, receiving modified or PK-tailored prophylaxis.
3) Section headings changed from 'Endpoints' to 'Outcome Measures'.
4) Descriptive statistics to be used for new outcome measures.
5) Order of secondary outcome measures rearranged.

Reason for changes:

1) To take the PK-tailored prophylactic treatment regimen into account.
2) A new exploratory outcome measure was added with the objective to explore potential correlation between TGA parameters, FIX activity levels and the occurrence of bleeds in subjects receiving prophylactic treatment.
3) To comply with the terminology of the new protocol template.
4) To describe how the exploratory outcome measure will be statistically analyzed.
5) To comply with a regulatory request.

21. Section 8.6.3: Description of Treatment

Description of changes:

1) Section split into '8.6.3.1 Prophylactic treatment with a subsection '8.6.3.1.1 PK-Tailored Prophylaxis', '8.6.3.2 Treatment of Bleeding Episodes' and '8.6.3.3 Surgery'.
2) It is emphasized that the dose should be adjusted according to the individual subject's age, the number of breakthrough bleeds, and/or the subject's physical activity; the previous text ('…may be adjusted at the discretion of the investigator…') was deleted.
3) Recommendation is provided to administer prophylactic infusions prior to increased physical activity.
4) New text added that in case of repeated bleeding despite revised treatment regimen an ultrasound of the affected joint should be performed to verify the presence of a bleed.
5) Criteria are provided when the treatment regimen has to be adapted.
6) The upper limit of the dose range is provided.
7) The procedures for PK-tailored prophylaxis are described.

Reason for changes:

1) To improve readability.
2) To underline that in case of breakthrough bleeds the treatment regimen must be adapted according to protocol.

3 & 5) To provide instruction to improve protection against bleeding episodes.

4) To verify whether the symptoms are the result of a bleeding episode or arthritic pain, if it occurs in subjects with target joints and/or hemophilic arthropathy.
6) To provide guidance for adjustment of treatment.
7) To provide information about the approach for the PK-tailored dose regimen and the PK.

22. Section 8.6.3.2: Treatment of Bleeding Episodes
Section 11.3: Hemostatic Efficacy

Description of changes:

1) The following text was added:

   "It is critical to inform the subject that "resolution of bleed" means "cessation of bleed" and not "cessation of all bleed related symptoms". This text refers to the patient diary (Section 11.3).

   'Certain underlying clinical conditions and/or the severity of the bleed may warrant an adjustment from these recommendations. In such a case, the reasons and need for changing the treatment approach should be recorded in the "General Comments" section of the eCRF. Additional infusions may be given to maintain hemostasis and until bleed-related symptoms have resolved.´ (Section 8.6.3.2)

   `It is important to clearly indicate after which infusion the bleed stopped (sentence highlighted). This may not necessarily coincide with the cessation of objective signs of bleeding, such as pain or swelling, since the absorption of blood would still be ongoing. Particularly in the case of severe hemophilic arthropathy and/or previous joint surgery combined with severe bleeds, it is more difficult to define exactly the time point of the cessation of the bleed. If pain persists despite several infusions of BAX326, the presence of a bleed should be verified. (Sections 8.6.3.2 and 11.3)

   It is also recommended to verify the presence of a joint bleed by ultrasound if despite several infusions of BAX326 the pain persists (Section 8.6.3.2)

2) The sentence "The frequency of BAX326 administration should not be less than twice weekly" was removed (Section 8.6.3.2).

Reason for changes:

1) To provide more detailed guidance on the treatment and documentation of bleeding episodes, in particular to distinguish between cessation of bleed and resolution of bleed-related symptoms. It is also recommended to verify the bleed if pain persists despite several infusions of BAX326.
2) This sentence was removed as it is not applicable in the section for treatment of bleeding episodes.

23. Section 8.8: Data Recorded Directly on Case Report Forms

Description of change:
The sentence was removed.

Reason for change:
The sentence was erroneously added since direct data entry is not considered as source data.

24. Section 3 Synopsis: Inclusion and Exclusion Criteria
Section 9.1: Inclusion Criteria
Section 9.2: Exclusion Criteria

Description of change:
Inclusion and exclusion criteria have been added for subjects who will be newly recruited to the study.

Reason for change:
To provide eligibility criteria for inclusion into the PK-tailored, once-weekly prophylactic dosing group for newly recruited subjects.

25. Section 9.3 Withdrawal and Discontinuation
Section 10.6 Subject Completion/Discontinuation

Description of changes:
1) The reason for withdarawal will be recorded on the Completion/Termination eCRF instead of the protocol deviation CRF.
2) The term “Discontinuation” was replaced by “Termination”.

Reason for change:
To be consistent within the protocol and with other protocols.

26. Section 10.3: Screening and Study Visits

Description of change:

Section split into two subsections describing the screening and study visits for subjects transitioning from the pivotal or pediatric study (Section 10.3.1) and newly recruited subjects (Section 10.3.2). In contrast to the transitioning subjects, the newly recruited subjects will undergo the full screening process: 'All screening/baseline evaluations must be completed within 42 days or repeated if more than 42 days have elapsed. Exemptions may be granted for administrative reasons by the sponsor, eg, delay in availability of laboratory results. For the purpose of analysis, only the data from the most recent screening visit will be used. If a subject does not satisfy all screening criteria, the same subject may be re-screened at a later date. A complete or partial re-screen may also become necessary at the discretion of the investigator or sponsor. All screening data will be collected and reported in eCRFs, regardless of screening outcome.'

Subjects should not be actively bleeding at the time of screening and at the scheduled study visits, and a wash-out period of at least 5 days, preferably 7 days, should be observed.'

Also some sections were regrouped for reasons of clarity.

Reason for change:

To describe the procedures for screening and study visits for newly recruited subjects and to improve clarity.

27. Section 10.5: Subject Diary

Description of changes:

1) It is emphasized that the investigator has to discuss at each study visit the diary entries with the subject, and ensure that all necessary information is correctly entered. Any unclear or implausible information should be immediately clarified with the subject at each study visit and instructions related to treatment and data entry be reinforced.
2) The option to replace the currently used paper diaries by electronic diaries.

Reason for changes:

1) To emphasize and ensure timely and correct transcription of requested data from diary to eCRF as well as to reinforce the importance that re-training of subjects may become necessary in terms of treatment and recording of data.
2) To facilitate data entry and ensure timely access to data and monitoring.

28. Section 11.1: Determination of FIX Activity
Section 21.2: Flow Diagram of Study Procedures
Section 21.4: Clinical Laboratory Assessments

Description of changes:

1) A general statement was added to emphasize that only 500 IU potencies for PK and IR determination should be used and that the dose is to be rounded up or down to the nearest whole vial in subjects ≥ 12 years whereas it should NOT be rounded in subjects < 12 years.
2) The section was split into various subsections to take into account 1) the newly recruited subjects who have a slightly different schedule, and 2) the additional abbreviated PK for the PK-tailored prophylactic dose regimen over 72 h (30 minutes pre-infusion and at 15 ± 5 minutes, 6-12 h, 18-30 h, 42-54 h and 66-72 h post-infusion of 75 ± 5 IU/kg BAX 326).
3) The determination of additional pre- and post-infusion FIX level determinations at 4-6 additional time points over a 6-months period (ie, in addition to the IR performed at regular study visits) is a newly introduced assessment for approximately 20 subjects receiving twice-weekly standard prophylaxis and all (or approximately 20) subjects receiving modified or PK-tailored dosing. The testing can be done any time in a 6-month period without the requirementof a wash-out period and should reflect the various dosing intervals of 2-7 days.

Reason for changes:

1) To ensure a dose range of 70 to 80 IU/kg for PK and IR determination for different age ranges and to ensure that only 500 IU potency vials from the same lot are used.
2) To provide the schedule for newly recruited subjects and exact time points for the PK determination.
3) To determine the trough FIX activity levels in approximately 40 subjects receiving various prophylactic treatment regimens and to explore whether these FIX activity levels provide sufficient protection against bleeding episodes.

29. Section 11.2: TGA Testing
Section 21.2: Flow Diagram of Study Procedures
Section 21.4: Clinical Laboratory Assessments

Description of changes:

1) New section added to describe TGA testing. This is to be done at the same timepoints as for FIX activity testing in approximately 20 subjects receiving twice-weekly standard prophylaxis over a 6-month period and in all subjects (or approximately 20) receiving modified or PK-tailored treatment regimen. This includes the determination of TGA parameters during PK and IR for FIX. TGA determinations are only to be performed in subjects ≥ 12 years of age.
2) Instructions on the blood volume for blood sampling is provided and reference made to the Laboratory Manual for the exact blood sampling procedures and processings.

Reason for changes:

1) To provide guidance regarding the exact timepoints for determination of TGA parameters as well as emphasizing that TGA testing is not performed in children < 12 years of age.
2) To ensure appropriate and correct pre-analytical blood sampling procedures and storage.

30. Section 11.3: Hemostatic Efficacy

Description of change:

The once-weekly PK-tailored prophylactic treatment at a dose up to a maximum of 120 IU/kg was added to the list of other possible treatment options to be assessed in terms of hemostatic efficacy.

Reason for change:

To provide details of the PK-tailored dose regimen.

31. Section 12 and subsections: Assessment of Safety

Description of changes:

Section updated according to revised protocol template (dated 27 September 2012); new text related to study conduct added as appropriate:

1) New section '12.2 Urgent Safety Matters' added which explains that the investigator may immediately, and without prior authorization from Baxter, take appropriate urgent safety measures in order to protect subjects against any immediate hazard, and how the sponsor should subsequently be notified.
2) Section 12.2.3 Causality: Sentence added: 'For each AE assessed as not associated or unlikely associated the investigator shall provide an alternative etiology.'
3) New section '12.2.5 Unexpected Adverse Events' added which defines unexpected AEs as AEs whose nature, severity, specificity, or outcome are not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert).
4) Section 12.2.6 Untoward Medical Occurrences Not Considered Adverse Events: The following text was added:
   'Each **serious** untoward medical occurrence experienced before the first IP exposure (eg, from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAE Report. These events will not be considered as SAEs or included in the analysis of SAEs.
   For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.'
5) New section '12.2.7 Non-Medical Complaints (NMCs)' added which defines an NMC as 'any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE'.
6) Section 12.2.8 Assessment of Adverse Events:
   The following sentence was added:
   'If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness.'

Reason for change:

To comply with the revised safety sections in the latest protocol template.

32. Section 12.3: Medical, Medication, and Non-Drug Therapy History Table 21.3-1, footnote b

Description of change:

One paragraph added: 'Any AE which has occurred in the BAX 326 pivotal or pediatric study and is still present at the time of enrolment to the current study will be considered as an "ongoing AE" and not as Medical History and will be recorded accordingly in the respective AE eCRF. Also, data on ongoing drug and non-drug therapy of these subjects will be used from the eCRF of these studies, updated, if applicable, and transcribed into the respective eCRF of the continuation study.

Reason for change:

To provide guidance on how to handle ongoing AEs, drug and non-drug therapy when transitioning into the Continuation study.

33. Section 12.4: Physical Examinations

Description of changes:

1) This section was updated according to the revised protocol template (dated 27 September 2012) to give guidance regarding evaluation and recording of new or worsening findings that are not deemed AEs: 'If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.2.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record'.
2) The definition for target joints was slightly revised. Subjects have to be examined for the occurrence of target joints every 3 months.

Reason for changes:

1) To be consistent with the revised section in the protocol template.
2) To take the long duration of the study into account.

34. Section 12.5.1: Immunology Tests
Section 12.5.3: Hematology and Clinical Chemistry
Section 12.5.4: Urinalysis
Section 12.5.5.1 Other Laboratory Tests at Screening
Section 12.6: Vital Signs

Description of change:
Schedule split in two sets of subjects to account for the newly recruited patients who have safety and immunology testing performed at screening (for newly recruited subjects), at visit week 4±1, month 3± 1 week, and thereafter every 3 months ± 1 week. Vital signs are also to be assessed. In addition, an IR and immunology assessments have to be performed at ED1.

Reason for change:
To describe the schedule of laboratory testing for newly recruited subjects.

35. Section 12.5.5.2: Biobanking

Description of change:
Previous section heading 'Back-up Samples' relabeled as 'Biobanking'. Additional information added regarding storage and testing beyond the end of the study.

Reason for change:
To be consistent with the revised protocol template and provide information about the timepoint when blood samples will be destroyed.

36. Section 12.5.6: Assessment of Abnormal Laboratory Values
Section 12.6: Vital Signs

Description of change:
Text adjusted regarding abnormal values not considered AEs.

Reason for change:
To be consistent with the revised protocol template.

37. Section 13: Assessment of Health-related Quality of Life and Health Resource Use

Description of change:

1) The rationale was updated.
2) It was specified when HrQoL and Health Resource Use was to be captured for newly recruited subjects.
3) It was also specified that in case subjects transition to an older age cohort, the same HrQoL questionnaires are to be used.

Reason for change:

1) To take into account the prolonged period of observation.
2) To provide a schedule for HrQoL and Health Resource Use assessment for newly recruited subjects and to provide guidance which age specific HrQoL questionnaires are to be used.
3) To provide guidance as to which questionnaire is to be used for subjects moving into an older age group.

38. Section 14.3.2.2 Pharmacokinetics

Description of change:

Text was added regarding the calculation of PK parameters for subjects planned to receive a PK-tailored treatment regimen.

Reason for change:

To provide information regarding the calculation of PK parameters for subjects reciving a PK-tailored treatment regimen.

39. Section 21.2: Flow Diagram of Study Procedures

Section 21.3: Schedule of Study Procedures and Assessments for Subjects Transitioning from 250901 or 251101

Section 21.4: Schedule of Study Procedures and Assessments for Newly Recruited Subjects –NEW

Section 21.5: Clinical Laboratory Assessments

Section 21.6 Clinical Laboratory Assessments for Newly Recruited Subjects – NEW

Section 21.7 Abbreviated PK Study for Subjects Receiving PK-Tailored Prophylaxis - NEW

Description of change:

Details of procedures for newly recruited subjects, the new PK-tailored prophylactic treatment regimen, and collection of TGA measurements added to flow diagram, study procedures and (laboratory) assessments.

Reason for change:

To provide the study procedures for newly recruited subjects, for the PK-tailored prophylactic treatment regimen and TGA testing.

SUMMARY OF CHANGES

BAX326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level ≤ 2%) Hemophilia B – A Continuation Study

Short Title: BAX 326 Continuation

PROTOCOL NUMBER: 251001

AMENDMENT 3 (UK AMENDMENT) VERSION: 28 December 2011

In this section, changes from the previous UK-specific version of the Protocol, Amendment 1 (UK Amendment), dated 08 July 2011, will be described and their rationale will be given.

Amendment 3 (UK Amendment) is identical to the global Amendment 2 (07 December 2011), with the exception of the study duration per subject (and consequently also the study completion date), which is a total of at least 150 exposure days to BAX326 in the UK (Pivotal/Pediatric and Continuation studies combined), as requested by the British MHRA.

1. Throughout the Document

Minor grammatical and/or administrative changes have been made to improve the readability and/or clarity of the protocol.

2. Section 3 Synopsis, Subsection: Completion

Description of change: The following clarification was provided regarding the completion date (which was previously stated to be approximately Q3 2014):
"Last Subject Out in the UK anticipated for approximately Q2 2014. Overall study completion (including all participating countries) anticipated for approximately Q1 2015."

Reason for change: The completion date of the study in the UK will be different than in the rest of the world since patients in the UK will be in the study for only approximately 100 exposure days.

3. ***Section 3 Synopsis, Subsections: Duration, Objectives, Study Design, Health-Related Quality of Life and Pharmacoeconomic Parameters, Investigational Product, Planned Number of Subjects, Inclusion/Exclusion Criteria, Planned Statistical Analysis***
   Section 6.1 Description of Investigational Product
   Section 6.3 Population to be Studied
   Section 7.1 Study Purpose
   Section 7.2 Study Objectives
   Section 8 Study Design
   Section 8.3.2.4 Health-Related Quality of Life and Health Resource Use
   Section 8.6.3 Description of Treatment
   Section 9.1 InclusionCcriteria
   Section 9.2 Exclusion Criteria
   Section 10.3 Screening and Study Visits
   Section 11.3 Hemostatic Efficacy
   Section 12.4 Clinical Laboratory Parameters
   Section 12.4.5.2 Back-up Samples for Further Testing
   Section 13.2 Health-Rrelated Quality of Life and Health Resource Use
   Section 14.3 Methods of Analysis
   Section 21.1 Study Flow Chart
   Section 21.2 Flow Diagram of Study Procedures
   Section 21.3 Schedule of Study Procedures and Assessments

   Description of change: The design was changed so that subjects taking part in the pediatric study (#251101) could be recruited into the continuation study. This includes the following changes:

   - Addition of background information concerning dosing and literature review of use in pediatric patients.
   - Increase in the number of patients to be included to up to 100.
   - Health-related quality-of-life (HR QoL) parameters relevant to the pediatric population were added.
   - The upper end of the dose range was listed as 80 IU/kg for pediatric subjects, and the IR used to calculate the required number of units to treat a bleeding episode was given as 0.7, as compared to 0.8 for subjects ≥ 12 years old.
   - Optional back-up samples for pediatric subjects
   - Total study duration and maximum study duration per subject extended from 43 to 48 months

- The pediatric (< 12 years) and the adolescent/adult (≥ 12 years) data will be summarized separately, if appropriate. Further analyses will occur between the age cohorts < 6 years and 6 to < 12 years, if applicable.

Reason for change: To enable pediatric subjects to continue to receive BAX 326 beyond the end of the main pediatric study (Study 251101).

4. Section 6.5 Relevant Literature and Data

This section was deleted to comply with the revised protocol template. Any relevant information is provided in Section 6.1.

5. Section 6.5 (previously 6.6) Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Description of Change: Information was added that the data on pharmacokinetics (PK) and safety of 16 subjects who had completed the PK cross-over part in the pivotal study had been reviewed by an external Data Safety Monitoring Committee and that overall, the data showed a PK profile comparable to BeneFIX and an acceptable safety and efficacy profile.

Reason for change: Study information update

6. *Section 3 Synopsis Inclusion Criteria*
Section 9.1 Inclusion Criteria

Description of Change: The inclusion criterion "The subject has severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) hemophilia B (based on the one stage activated partial thromboplastin time (aPTT) assay), as tested at screening at the central laboratory" was deleted.

Reason for change: The required severity of hemophilia B (FIX level ≤ 2%) which is determined by the type of gene mutation has been confirmed at screening for either BAX326 pivotal or BAX 326 pediatric and is not subject to change. Therefore it is superfluous for the continuation study.

7. ***Section 8.1 Overall Study Design***
Section 21.1 Study Flow Chart
Section 21.2 Flow Diagram of Study Procedures
Section 21.3 Schedule of Study Procedures and Assessments
Section 21.4 Clinical Laboratory Assessments

Description of change: The visit window for those subjects switching back to the continuation study from the surgery study was extended from ± 1 week to ± 2 weeks.

Reason for change: To reduce protocol deviations relating to out-of-window visits following surgery.

8. ***Section 6.1 Description of Investigational Product***
Section 8.1 Overall Study Design
Section 8.6.3 Description of Treatment

Description of change: 1) Information of the clinical development program of BAX 326 was shortened and updated. 2) The definition of end of study for BAX 326 Surgery (Protocol 251002) was adapted according to a protocol amendment.

Reason for change: To reflect 1) the ongoing progress of the BAX 326 clinical development, and 2) protocol amendments.

9. ***Section 8.5 Study Stopping Rules***

Description of change: The wording for study stopping rules was slightly revised

Reason for change: To be consistent with the wording of the other BAX 326 protocols

10. ***Section 8.6.1 Packaging, labeling, Reconstitution, Storage, and Shelf-life***

Description of change: 1) Vials of a nominal potency of 250 IU and 3000 IU will be added during the course of the study. 2) Information on stability has been removed.

Reason for change: 1) To account for the availability of additional potencies. 2) Information on stability is provided in the BAX 326 Investigator's Brochure.

11. ***Section 10.3 Screening and Study Visits***

Description of change: Details are provided regarding laboratory tests in those subjects who are temporarily transitioned to BAX 326 Surgery (# Protocol 251002) and back to the main study.

Reason for change: To reduce the frequency of blood sampling.

12. ***Section 10.5 Subject Diary***

Description of change: It was added that the Investigator will evaluate whether the subject adheres to the prescribed treatment regimen.

Reason for change: To ensure that the protocol specific treatment regimen is followed.

13. ***Sections 11.3 and 14.3.5 Hemostatic Efficacy***

Description of change: 1)The clinical hemostatic efficacy ratings at 12 ± 1 hours and 24 ± 1 hours following infusion of BAX 326 were deleted. 2) Additional guidance to review the efficacy ratings by the investigator is provided.

Reason for change: Use of the 12 h and 24 h timepoints are exploratory in nature and only used in BAX 326 Pivotal (#250901), but not in BAX 326 Pediatrics (#251101). The change is implemented to harmonize the efficacy rating timepoints with those used in the BAX 326 pediatric study (#251101). 2) To emphasize the importance to review the diary, the treatment of bleeding episodes and the efficacy evaluations.

14. ***Section 22 References***

Description of change: Reference 2 was replaced with the newly adapted EMA guideline.

Reason for change: To update the reference of the newly adapted EMA guidelines.

SUMMARY OF CHANGES

BAX 326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level ≤ 2%) Hemophilia B – A Continuation Study

Short Title: BAX 326 Continuation

PROTOCOL NUMBER: 251001

AMENDMENT 2 VERSION: 07 December 2011

In this section, changes from the original version of the Protocol, dated 28 October 2010, will be described and their rationale will be given. (Amendment 1, dated 08 July 2011, was an amendment specific to the UK and consisted of only one change regarding the study duration per subject which was requested by the British MHRA.)

1. ***Throughout the Document***

   Minor grammatical and/or administrative changes have been made to improve the readability and/or clarity of the protocol.

2. ***Section 3 Synopsis, Subsections: Duration, Objectives, Study Design, Health-Related Quality of Life and Pharmacoeconomic Parameters, Investigational Product, Planned Number of Subjects, Inclusion/Exclusion Criteria, Planned Statistical Analysis***
   Section 6.1 Description of Investigational Product
   Section 6.3 Population to be Studied
   Section 7.1 Study Purpose
   Section 7.2 Study Objectives
   Section 8 Study Design
   Section 8.3.2.4 Health-Related Quality of Life and Health Resource Use
   Section 8.6.3 Description of Treatment
   Section 9.1 InclusionCcriteria
   Section 9.2 Exclusion Criteria
   Section 10.3 Screening and Study Visits

Section 11.3 Hemostatic Efficacy
Section 12.4 Clinical Laboratory Parameters
Section 12.4.5.2 Back-up Samples for Further Testing
Section 13.2 Health-Rrelated Quality of Life and Health Resource Use
Section 14.3 Methods of Analysis
Section 21.1 Study Flow Chart
Section 21.2 Flow Diagram of Study Procedures
Section 21.3 Schedule of Study Procedures and Assessments

Description of change: The design was changed so that subjects taking part in the pediatric study (#251101) could be recruited into the continuation study. This includes the following changes:

- Addition of background information concerning dosing and literature review of use in pediatric patients.
- Increase in the number of patients to be included to up to 100.
- Health-related quality-of-life (HR QoL) parameters relevant to the pediatric population were added.
- The upper end of the dose range was listed as 80 IU/kg for pediatric subjects, and the IR used to calculate the required number of units to treat a bleeding episode was given as 0.7, as compared to 0.8 for subjects ≥ 12 years old.
- Optional back-up samples for pediatric subjects
- Total study duration and maximum study duration per subject extended from 43 to 48 months
- The pediatric (< 12 years) and the adolescent/adult (≥ 12 years) data will be summarized separately, if appropriate. Further analyses will occur between the age cohorts < 6 years and 6 to < 12 years, if applicable.

Reason for change: To enable pediatric subjects to continue to receive BAX 326 beyond the end of the main pediatric study (Study 251101).

3. Section 6.5 Relevant Literature and Data

This section was deleted to comply with the revised protocol template. Any relevant information is provided in Section 6.1.

4. ***Section 6.5 (previously 6.6) Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects***

   Description of Change: Information was added that the data on pharmacokinetics (PK) and safety of 16 subjects who had completed the PK cross-over part in the pivotal study had been reviewed by an external Data Safety Monitoring Committee and that overall, the data showed a PK profile comparable to BeneFIX and an acceptable safety and efficacy profile.

   Reason for change: Study information update

5. ***Section 3 Synopsis Inclusion Criteria***
   Section 9.1 Inclusion Criteria

   Description of Change: The inclusion criterion "The subject has severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) hemophilia B (based on the one stage activated partial thromboplastin time (aPTT) assay), as tested at screening at the central laboratory" was deleted.

   Reason for change: The required severity of hemophilia B (FIX level ≤ 2%) which is determined by the type of gene mutation has been confirmed at screening for either BAX326 pivotal or BAX 326 pediatric and is not subject to change. Therefore it is superfluous for the continuation study.

6. ***Section 8.1 Overall Study Design***
   Section 21.1 Study Flow Chart
   Section 21.2 Flow Diagram of Study Procedures
   Section 21.3 Schedule of Study Procedures and Assessments
   Section 21.4 Clinical Laboratory Assessments

   Description of change: The visit window for those subjects switching back to the continuation study from the surgery study was extended from ± 1 week to ± 2 weeks.

   Reason for change: To reduce protocol deviations relating to out-of-window visits following surgery.

7. ***Section 6.1 Description of Investigational Product***
Section 8.1 Overall Study Design
Section 8.6.3 Description of Treatment

Description of change: 1) Information of the clinical development program of BAX 326 was shortened and updated. 2) The definition of end of study for BAX 326 Surgery (Protocol 251002) was adapted according to a protocol amendment.

Reason for change: To reflect 1) the ongoing progress of the BAX 326 clinical development, and 2) protocol amendments.

8. ***Section 8.5 Study Stopping Rules***

Description of change: The wording for study stopping rules was slightly revised

Reason for change: To be consistent with the wording of the other BAX 326 protocols

9. ***Section 8.6.1 Packaging, labeling, Reconstitution, Storage, and Shelf-life***

Description of change: 1) Vials of a nominal potency of 250 IU and 3000 IU will be added during the course of the study. 2) Information on stability has been removed.

Reason for change: 1) To account for the availability of additional potencies. 2) Information on stability is provided in the BAX 326 Investigator's Brochure.

10. ***Section 10.3 Screening and Study Visits***

Description of change: Details are provided regarding laboratory tests in those subjects who are temporarily transitioned to BAX 326 Surgery (# Protocol 251002) and back to the main study.

Reason for change: To reduce the frequency of blood sampling.

11. ***Section 10.5 Subject Diary***

Description of change: It was added that the Investigator will evaluate whether the subject adheres to the prescribed treatment regimen.

Reason for change: To ensure that the protocol specific treatment regimen is followed.

12. ***Sections 11.3 and 14.3.5 Hemostatic Efficacy***

Description of change: 1)The clinical hemostatic efficacy ratings at 12 ± 1 hours and 24 ± 1 hours following infusion of BAX 326 were deleted. 2) Additional guidance to review the efficacy ratings by the investigator is provided.

Reason for change: Use of the 12 h and 24 h timepoints are exploratory in nature and only used in BAX 326 Pivotal (#250901), but not in BAX 326 Pediatrics (#251101). The change is implemented to harmonize the efficacy rating timepoints with those used in the BAX 326 pediatric study (#251101). 2) To emphasize the importance to review the diary, the treatment of bleeding episodes and the efficacy evaluations.

13. ***Section 22 References***

Description of change: Reference 2 was replaced with the newly adapted EMA guideline.

Reason for change: To update the reference of the newly adapted EMA guidelines.

SUMMARY OF CHANGES

BAX 326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level ≤ 2%) Hemophilia B – A Continuation Study

Short Title: BAX 326 Continuation

PROTOCOL NUMBER: 251001

EudraCT Nr: 2010-022726-33

AMENDMENT 1 (UK AMENDMENT) VERSION: 08 JULY 2011

In this section, changes from the original Protocol, dated 28 October 2010, will be described and their rationale will be given.

1. ***Throughout the Document***

   Minor grammatical and/or administrative changes have been made to improve the readability and/or clarity of the protocol.

2. ***Section 3 Synopsis Duration***
   Section 3 Synopsis Objectives
   Section 3 Synopsis Planned Duration of Subject Participation
   Section 6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects
   Section 8.2 Duration of Study Period(s) and Subject Participation
   Section 21.1 Flow Chart
   Section 21.2 Flow Diagram of Study Procedures

   Description of change: 1) The option that subjects could stay in the study until BAX 326 is licensed in his/her country had to be deleted. The study duration per subject will be approximately 12 months until the subject has accumulated a total of at least 150 EDs to BAX 326 in both the BAX 326 pivotal (250901) and BAX 326 continuation (251001) study. Therefore, the total number of accumulated EDs was increased from 100 to 150 EDs.

   Reason for change: 1). The change was made upon request by the MHRA.